ScienceMind

SUMMER 2023

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THIS ISSUE

Dear Reader,

Welcome or welcome back to another year at King's!

Over the break, ScienceMind members have been working hard to create a new Summer 2023 issue! We hope you enjoy reading it as much as we've enjoyed creating it. This issue has articles in the categories of physics, aerospace, immunology, neuroscience, physical chemistry, evolutionary biology, genetics, biotechnology, and technology.

On another front, the ScienceMind podcast is now up and running, with the first episode already out! Tune in on Spotify, Apple Music, or any other preferred listening platform to hear from the KCL iGEM team about their exciting synthetic biology project for the prestigious iGEM competition, hosted by our talented co-heads, Elina and Eaint.

This year, we're looking forward to reinvigorating ScienceMind's community spirit, so if you're interested in any aspect of STEM or design, join us for our Welcome to ScienceMind picnic. Follow us on social media and sign up to our newsletter for location and time updates.

If this is your first time reading our magazine...

ScienceMind is the award-winning, student-led science magazine of King's College London. We report the latest findings in STEM to students and the wider community. We showcase and develop the written and oral communication skills of students interested in STEM by concisely explaining complex scientific concepts in the form of lay articles and by conducting interviews. Authors can also broaden their knowledge by writing articles for different sectors between issues.

Articles have difficulty levels. There's something for everyone!
Shallow dive: Secondary school level
Treading water: A-level to undergraduate level
Deep dive: Final year undergraduate, postgraduate, professor level

ScienceMind is ever growing, join the new age of science media.

Kind regards,

Olivera Mitevska

Editor-in-Chief
Olivera Mitevska

He Jiankui: Genome editing to achieve HIV immunity

WRITTEN BY HELENA BRADBURY
EDITED BY SAMUEL GINZBURG
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In November 2018 Chinese biophysicist, **He Jiankui**, shocked the scientific community by announcing the world's first **gene-edited babies**. The twin girls, under pseudonyms **Lulu and Nana**, had been **genetically modified** using **CRISPR** technology to mimic the natural **CCR5-delta 32 mutation**, in an attempt to gain genetic immunity to HIV. However, after experimental details emerged it was found that he had induced varied mutations in the babies' genome and had not properly informed doctors and regulatory boards of his research at the time. With little known of the long-term implications of these edits, it raises the question of to what extent should gene editing technology act as a preventative medical treatment?

Figure 1: He Jiankui speaking at 2018 Human Genome gene-editing summit in Hong Kong

HIV is transmitted through contact with the **body fluids** of those infected, such as blood by exchange of **drug needle,** or by **sexual contact.** Upon **early infection (3-6 weeks)**, a patient typically experiences **flu-like symptoms** such as **fatigue** and **temper**, during which the virus enters an **incubation** period of **10+ years** during which the viral RNA copies gradually increase as more **CD4+ cells** are infected. Eventually, as the number of active immune cells falls, the patient becomes **immuno comprised,** leading to AIDs related diseases such as **Wasting Syndrome** and **Tuberculosis.** Structurally, the virus is comprised of a **lipid envelope,** made of **p24 protein,** with **glycoproteins gp120** and **gp41** that extend from the cell and bind with target immune cells.

Within the envelope is a **nuclear capsid** containing **essential enzymes** required for the **replication** and **transmission** of the virus, such as **reverse transcriptase**, as well as a nuclear capsid containing the **core RNA genome**. As a retrovirus, HIV relies on the **cellular machinery** of its host in order to **multiply** and does this by **reverse transcribing** its RNA genome into DNA that is then **integrated into** the **genome,** via **integrase**, for subsequent **translation** into new budding virions. An infected cell is subsequently **killed by caspase 1/3** mediated **pyroptosis** or by **cytochrome C** release in **mitochondrial apoptosis.**

For complete **HIV infection** to occur, a series of **fusion events** must occur between the virus and target immune cell. Firstly, the **gp160 glycoprotein**, composed of **gp120/41**, must **bind** the **CD4 surface receptor** of the cell which then triggers a **conformational change** in **gp120** exposing a **binding site, V3 loop segment**, for a secondary co-receptor to **anneal.** As HIV can infect several cell types, known as **tropism**, the **co-receptor** present **differs** among cells. For instance, **CCR5 (chemokine [C-C] motif receptor 5)** coreceptor binding is called **CCR5/R5 tropism**, whilst binding of a **CXCR4 (CXC chemokine receptor 4) is called X4/CXCR4**. CCR5 tropism is expressed on **memory T cells, macrophages** and **dendritic immune cells** whilst CXCR4 tropism is expressed on **B cells** and **eosinophils**, for example, and the ability to bind to either coreceptor is known as **dual tropism.** It is therefore crucial for HIV transmission, that binding occurs at both the CD4 receptor as well as the CXCR4/CCR5 coreceptor, depending on the cell type.

Figure 2: Schematic illustrating HIV tropism (A) CCR5 tropic virus annealing to CD4 receptor and CCR5 receptorexpressed on CCR5 cell such as T cell, macrophage or dendritic cell for example. (B) CXCR4 tropic virus annealing to CD4 receptor and CXCR4 coreceptor on CXCR4 cell such as B cells and eosinophils. (C) Zoomed in schematic showing conformational change of gp120 to expose V3 loop segment that then binds to coreceptors CCR5 or CXCR4.

Interestingly, a **mutation** called **ccr5-delta 32** causes the **CCR5 coreceptor** to develop smaller than usual, inhibiting the anchoring and infection of HIV. The homozygous mutation is common within **European and west Asian** populations and is estimated to have existed in humans from **700-2900 years**. The presence of the **gene mutation** through generations may be due to **natural selection**, providing survival advantages during pandemics such as the **Black Death** or **Smallpox**. For those homozygous to the mutation, it means an increased HIV immunity and was mimicked experimentally in 2018 by He Jiankui in a controversial attempt to achieve the same level of immunity from birth.
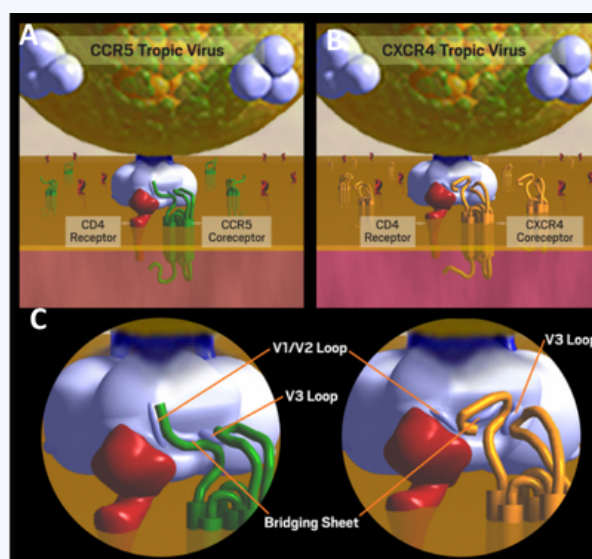
Many conventional treatments exist for HIV, with the most common being **antiretroviral therapy**, a combination of drugs taken that block each stage of the viral life cycle. Nucleoside reverse transcriptase inhibitors, for example, block the transcription of viral RNA to DNA and protease inhibitors prevent the creation of new viral particles. Whilst this form of therapy has improved patients quality of life, each HART drug class carries individual complications such as **neuropathy, increased stroke severity seizures and mitochondrial myopathies**. Gene editing therefore gave hope to an endogenous alternative therapy that carried fewer adverse effects.

He Jiankui attended the **University of Science and Technology of China** as an undergraduate from **2002-2006.** Following this, he received his **PhD from Rice University** from the **Department of Physics and Astronomy** in 2010 and worked as a research fellow at **Stanford University** working on CRISPR gene-editing techniques. In 2012, he returned to China as a professor at the **Southern University of Science and Technology** and founded several companies such as **Direct Genomics and Vienomics Biotech**. During his career he received numerous accolades such as the **'Chinese Government Award for Outstanding Self-financed Student Abroad'** and was widely respected among the research community. However, in **November 2018,** He announced that he had created gene-edited babies, known by pseudonyms **Lulu and Nana**, that mimicked the **CCR5-delta32 mutation** in hopes of achieving HIV immunity. Despite the good-willed intent, the scientific community were in outrage and three days following the announcement Chinese authorities **terminated** his research and sentenced him to **three years in prison.**

So why the outcry? You may ask. He tried to **eradicate HIV** infections, surely that is something to celebrate. In short, whilst the aim of **minimising HIV** spread was admirable it was the **ethical** and **experimental** grounds He was criticized on. The original paper remains **unpublished** however Antonio Regalado first released extracts for **MIT technology review**, and He later discussed the study at the international gene-editing summit in **Hong Kong.** It is known that the Chinese couple was suffering with **infertility** and the father was a **HIV-carrier**. After attending a conference held by He in 2017 the couple were offered **in vitro fertilisation** and **gene editing** to achieve **HIV immunity.** Being **HIV-positive** also carries a stigma in China and carriers of the virus are not allowed IVF treatment for infertility. It is therefore problematic that He promised IVF to a vulnerable patient group, that otherwise would not have been allowed to receive it, in exchange for their participation in his study. **'12 oocytes** were collected from the mother who was under **ovarian stimulation** prior to IVF fertility and the male's sperm was **washed through** to remove **infectious seminal fluid'** states the paper. **Sperm washing** is a common technique for HIV carriers and is done to remove the seminal fluid containing the **highest concentrations** of HIV. This means that the **gene editing** was not done to prevent. **vertical transmission,** between father and daughter, but instead from infection later in life.
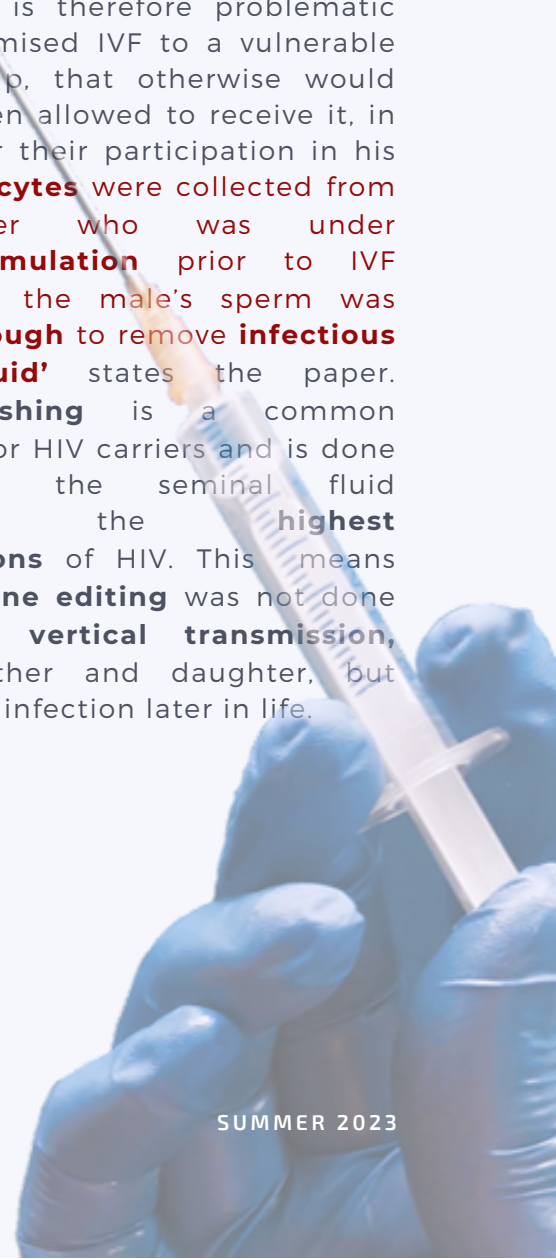
The paper then states that following fertilisation **Cas9 protein** and **gRNA** were **injected** into the cytoplasm of the **embryo** and after **5-6 days** in culture **four viable blastocysts** were obtained. CRISPR stands for **clustered regularly interspaced short palindromic repeats** and is technology invented by **Emmanuelle Charpentier** and **Jennifer A. Doudna,** earning them the **2020 Nobel prize for Chemistry**. It uses a short DNA sequence to bind and target specific, gRNA, and a nuclease called Cas9 to cleave the DNA once the target gene is bound. Once cleaved, the DNA will repair itself leading to small insertions or deletions in the process. The flexibility of CRISPR means that it can be used in many industries such as in **agriculture** to design more nutrient efficient crops or in **medicine** for pathogen detection and disease correction. Since its creation, adaptations have been made to the technology such as **SHERLOCK** (Specific High-sensitivity enzymatic reporter unlocking),a highly sensitive Cas13-based crispr that can detect from both RNA and DNA targets. Off-target mutation still remains a risk with these gene editing tools, however the use of gold nanoparticles or cationic liposomes are among some ways to increase Cas9 specifity.

Following CRISPR, the paper goes on to explain that the cells of the **IVF embryo** were removed, and their edits examined to check they **conferred** with the natural **ccr5-delta 32 mutation.** He writes, 'One embryo was edited on both CCR5 alleles, with each containing **frameshift mutations** that **deactivated** the **CCR5 protein.** We expect this to confer complete resistance to HIV-1 virus infection, similar to the natural **CCR5 delta 32 variation**'. This is incredibly concerning as it suggests that He induced a mutation that was not identical to the **CCR5 32 base deletion** in the embryos, instead **silencing** the CCR5 gene all together hoping it would have the same effect.

Moreover, Jiankui continues to write; 'the other embryo has one allele edited with a **15bp deletion**, and the other allele wildtype' meaning that a random **15 base pair deletion** was made to the other embryo despite there being no supporting experimental data to inform this decision. Furthermore as it was only one allele, even if it was successful it would only guarantee **partial resistance** to HIV. **Off-target mutations** can also occur from genome single-cell sequencing, and He states that only **one 1 bp insertion** was detected **(chr1:69754212)** but this data was from cells taken from the **early-embryo** and not from cells that ultimately formed the **mature babies.** From chromatograms released in the supplementary material, it is clear that Lulu and Nana also exhibited **mosaicism,** meaning that edits throughout the embryos were **not uniform**. As a result, there is no way of knowing for sure what **off-target mutations** were made in each cell of the twins and the implications both the intended, and off-target edits will have on the **development** and **function** of the babies as they grow up. It is staggering to consider that instead of testing these edits on **frozen human** or **animal cells** in the laboratory over time, these preliminary research stages were ignored and tested for the first time in **human embryos.** This case serves an essential cautionary tale in using **CRISPR** and other gene editing tools in research and the regulation that must be upheld when experimenting with them.

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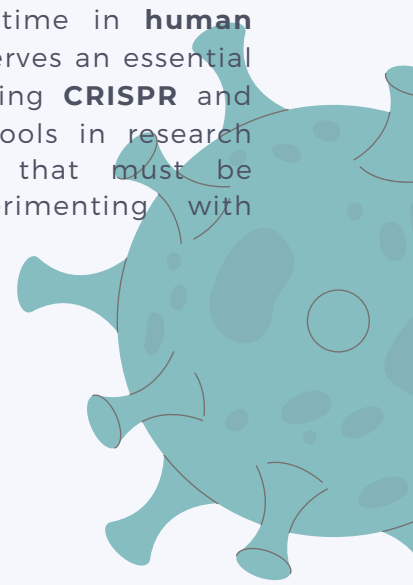
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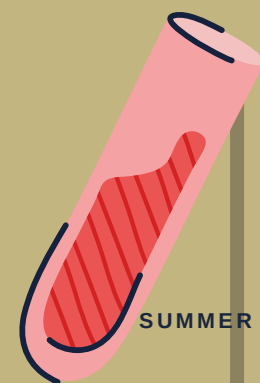
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SHALLOW DIVE

From **Forbes** youngest self-made female billionaire worth $4.5 billion in 2014 to a **convicted felon** in 2022 charged with four counts of **defrauding** investors. This was the reality for Elizabeth Holmes whose story has been **dramatized** in the Hulu series 'The Dropout' and **HBO's** 'The Inventor: Out for Blood'. At 19, Holmes **dropped out** of Stanford to pursue her medical startup, **Theranos**, claiming to have invented technology that could **revolutionise** the blood testing industry. The invention was called the **Edison test**, a small machine that could test for multiple **diseases** from a single drop of **blood**, compared to 30ml in a standard blood test. However, after initial success, **whistleblowers** began to question the authenticity of the device and Holmes, along with her **chief operator officer** and former boyfriend Ramesh 'Sunny' **Balwani**, were sentenced to 13 and 11 years respectively. This article will delve into the **mechanism** of the Edison and how **loopholes** in regulation allowed for the technology to become FDA approved despite **never working**. Finally, it will follow key events that led to the rise and fall of this former **Silicon Valley CEO.**

Elizabeth Holmes was born on February 3rd 1984 in Washington DC. Her father, **Christian Rasmus Holmes IV**, worked as the vice president of an **energy** company called **Enron** and her mother worked as a congressional committee staffer. She graduated from **St John's High School** and attended **Stanford** in 2002 to study chemical engineering. However, by 2004, Holmes **dropped out** and used her college tuition money to fund her **startup** initially called 'Real-Time Cures' in **Palo Alto**, California. The name was later converted to **Theranos**, a combination of the words 'therapy' and 'diagnosis'. In September 2009 **Balwani** loaned the company $10 million and became **chief operating officer** (COO).

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Prior to this, he had acted as President to the software startup **Commerce Bid** in 1999 and was able to leave the company with **$40 million** after it went bust.

The pair first met back in 2002 in **Beijing** China as part of a **Stanford** study programme and eventually began **dating**, Elizabeth was 18 at the time and Balwani 37. The pair maintains that their **relationship** was initially **platonic** as Balwani was still married to Japanese artist **Keiko Fujimoto** at the time, however, they later separated in 2002. At the time of their first meeting, Balwani was **enrolled** in an MBA program at the University of California, Berkley and Holmes was set to start her **freshman year** at Stanford University. Dating rumours of the pair began **circulating** after they purchased their first condo together in Palo Alto and by 2013, the couple had upgraded to a **$9 million home** in Atherton, California.

As an individual, Holmes has been described as **highly persuasive** and driven, raising over $700 million in funds from private investors and **venture capitalists**. However, it was not only the monetary value of **Theranos** that made its reputation in Silicon Valley but also its **influential** board of directors. They included **Henry Kissinger** (former United States Secretary of State), **William Perry** (former United States Secretary of Defence), **Richard Kovacevich** (former CEO of Wells Fargo), **William Foege** (former director of Centre for Disease Control and Prevention) and notably **George Shultz** (former United State Secretary of State) among others.

Oracle executive chairman **Larry Ellison**, Investor **Tim Draper** and American magnate **Rupert Murdoch** were also among investors, with Murdoch reportedly investing over **$100 million** between 2014-2015. With growing interest in the **company**, however, pressure was built to produce **working technology** that could be FDA-approved and begin **clinical trials.**

The **technology** invented by Theranos was called the **Edison** and would analyse **blood** from its **nanocontainer**. As shown in the image above, it was a **portable device** that was capable of allegedly running hundreds of **diagnostic tests** on a single drop of blood. For a standard blood test, a technician will tighten a **tourniquet** around a patient's arm and draw blood using a **needle syringe**. The blood vial is then sent to a laboratory and **immunoassays** are performed to check for allergies, genetic conditions or **infection**, among other things. **Autoimmune diseases**, for example, can be detected by elevated **complement C3** levels or **C-reactive protein**, whilst blood **glucose** levels correspond to **diabetes**. Specific **tumour markers** can also be measured in the blood such as alpha-fetoprotein for **liver cancer**, Ca-125 for **ovarian cancer** and calcitonin for **thyroid cancer**.
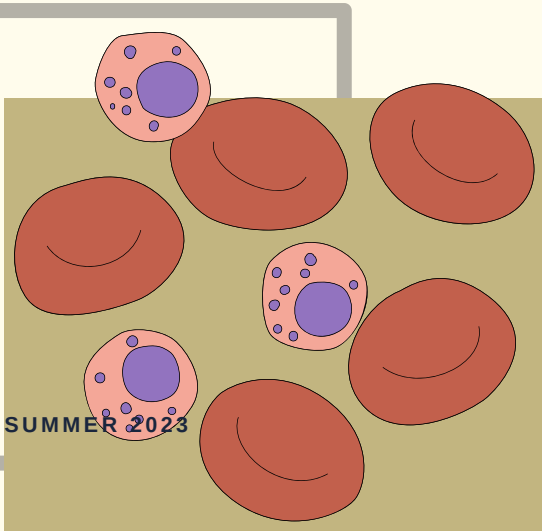
Whilst the **accuracy rate** of laboratory blood tests is high, the **time** taken for patients to receive blood test results can range from **days to weeks**, causing a **delay** in treatment and **diagnosis**. The Edison instead promised **immediate results**, a smaller **volume** of blood and the ability to perform numerous tests **simultaneously**. If successful it would have **accelerated** the blood testing **industry** forward by **10+ years** and provided in-store testing, following their 2013 partnership with **Walgreens**. But it did not work. In the 2021 trial, one woman **alleged** that her results indicated she was having a **miscarriage** when she wasn't whilst another woman was **falsely diagnosed** with HIV. A man also **testified** in the trial alleging that the test advised him to stop taking his **blood thinning medication** which could have caused him to have a **stroke**.

So if the **technology** didn't work how did it become **FDA approved**? The U.S. Food and Drug Administration categorizes devices from Class I, **low risk**, to Class III, **high risk**, with **greater regulations** associated with those of a higher class. In 2015, the FDA labelled the **nanocontainer** as a Class II technology, however, Theranos **continued** to distribute the device as Class I, claiming it was **wrongly classed**. Moreover, the device fell under the regulatory category of **laboratory-developed tests**, 'a type of in vitro diagnostic test that is designed, **manufactured** and used within a **single laboratory**'. Laboratory-developed tests are not required by the **FDA** to be pre-tested before going on the **market**. This allowed Theranos to exploit this **loophole** and avoid **early scrutiny**. In July 2015, the FDA approved the device as a diagnostic test for **herpes simplex 1 virus**. Interestingly, it was the **patent portfolio** of Theranos that revealed suspicious activity within the company long before the 2015

Wall Street Journal article was published. A **patent** is an exclusive right granted to an invention to prevent the making and use of one's invention by **another party**. The main classes of patents are: (1) **utility**, which protects the **functional** and **useful** aspect of the invention, (2) **design**, which protects the **visual qualities** of an item, and (3) **plant,** which protects new types of flowering plants that reproduce asexually. For an invention to be **successfully** patentable it must also meet the necessary **criteria** of being novel, useful and a non-obvious creation from the **prior art**. Moreover, the **enablement requirement** states that the patent application must provide **sufficient** detail for someone within the field to build the **working invention**. For Theranos, approximately **859 patents** were granted by the U.S. Patent and Trademark Office (**USPTO**) between the years **2003-2021**, with Elisabeth Holmes named as an **inventor** in 544.
If Holmes had in fact lied and inflated her involvement in these patents, it would be grounds for an intellectual property **lawsuit** for **misrepresentation** of inventorship.

A **review** of the patent history revealed that Theranos' **Edison machine** design was **rejected** several times by the Patent Office. Whilst this isn't uncommon for **inventions,** it is unusual for a company that has promised **multi-million** dollar investors groundbreaking technology. Moreover, the device was finally approved on the **condition** it contained a **cytometer**, an instrument used to detect the number of cells within a **population** and their **characteristics**. However, selling for over $30,000, cytometers, are **expensive instruments** that have a detrimental effect on the cost of the Edison and the company revenue.

theranos

| (12) | **United States Patent** | (10) | Patent No.: | US 8,435,738 B2 |
| | Holmes | (45) | Date of Patent: | May 7, 2013 |

(54) **SYSTEMS AND METHODS FOR MULTI-ANALYSIS**

(75) Inventor: **Elizabeth Holmes**, Palo Alto, CA (US)

(73) Assignee: **Theranos, Inc.**, Palo Alto, CA (US)

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These **early warning signs** reinforce the importance of **patent literacy**, as patents reveal information about a company's **proposed technology** that can otherwise be concealed from investors and the media. The **legal issues** of Theranos worsened in 2011 when **Richard Fuisz**, founder of Fuisz Technologies Ltd, and former family friend of Holmes, was **sued** by the company for **misappropriating** a Theranos patent. In 2007, Fuisz had filed a patent for a **data storage unit** that would alert physicians of blood test results if a set **threshold** value was **exceeded**. As a basic premise, this would allow him to collect **royalties when inevitably used by the company.**. However, backed by famed litigator **David Boies**, Holmes fought the case claiming Fuisz stole confidential information to rival Theranos, and a settlement was eventually reached.

The **downfall** of the company began in October 2015 when **Wall Street Journal** reporter **John Carrey Rou** published a report that Theranos was using **standard laboratory measures** to generate their results instead of the Edison technology. Subsequently, in November 2015, despite investing **$350 million** into building in-store clinics, American **supermarket** chain Safeway terminated its **partnership** with Theranos following failed clinical trials and growing speculation. In July 2016, a **regulatory** organisation, **Centres for Medicare and Medicaid Services**, ordered Theranos' California lab to be closed following **inspection**, stating it '**failed to comply** with federal standards and that patients are in **immediate jeopardy**'.

 Holmes was also **banned** by CMS from running a blood-testing lab for 2 years. In the month prior, **Walgreens** also ended its **partnership** with the company **closing** all 40 in-store Wellness Centres and later **sued** the company in November 2016 for **breach of contract.** Over 500 employees were laid off between the months of October 2016-Janurary 2017. By June 2018, Holmes and Balwani were **indicted** on **criminal fraud charges**. Fast forward to the subsequent year, January 2022, and Holmes is **found guilty** of one count of conspiracy to defraud investors and three **wire fraud** counts. Balwani was found guilty of ten counts of federal wire fraud and two counts of **conspiracy** to commit wire fraud, with both facing up to **twenty years in prison.**
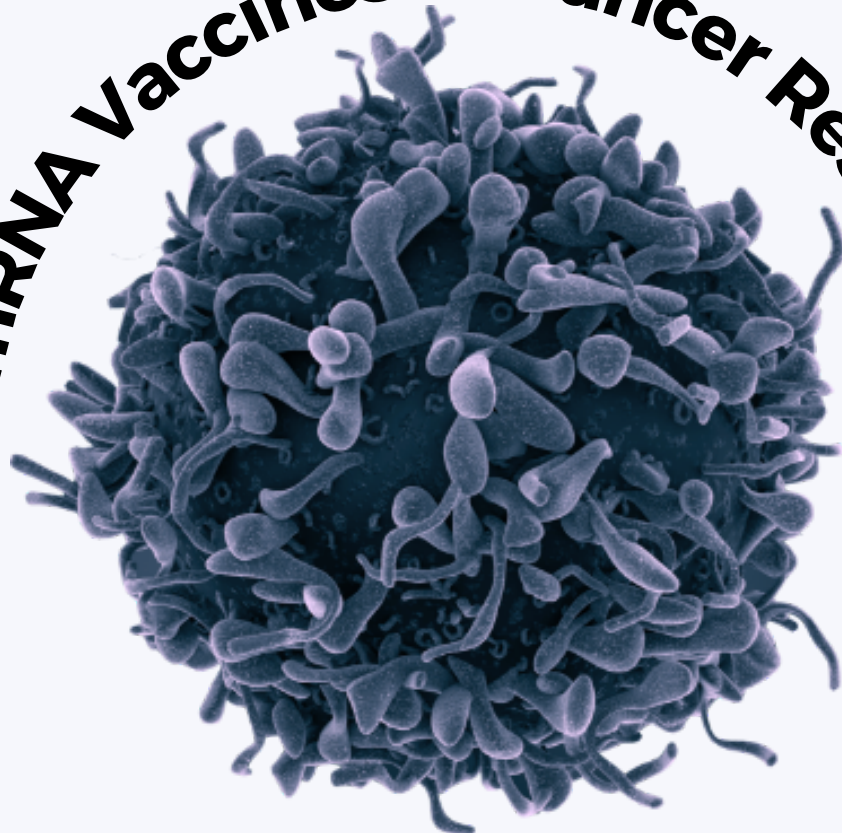
References

DEEP DIVE

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DESIGNED BY ASHNA SURANA

mRNA Vaccines in Cancer Research

Introduction

According to the **World Health Organization,** cancer is one of the primary reasons for **mortality** worldwide [1]. Its treatment includes several **therapeutic strategies**, among which are **cancer vaccines** as a form of **immunotherapy** [2]. It is focused on **stimulating** the host's own immune system to produce **tumour-related antigens** with the goal of **tumour shrinking** and **improved patient health** [3]. Research in this field has rather been slow and difficult due to the large variety of cancer types and antigens that could be produced. However, there has recently been a **major improvement**. The **severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)** infection outbreak in the beginning of 2020 which resulted in a **coronavirus 2019 (COVID-19) pandemic** [4] have brought significant acceleration to the research and development of effective and safe **mRNA vaccines**. Next-generation therapies such as **RNA vaccines** have been a promising choice of treatment in the battle against COVID-19 due to the need for rapid development, effectiveness, and safety which could not be as easily achieved with conventional vaccines such as live attenuated or **inactivated vaccines** [2]. The development and approval of **two mRNA-based COVID-19 vaccines** [5, 6] increased the interest of research on the opportunities to use these vaccines in cancer therapeutics. In this report, mRNA vaccines for **cancer research** are explored in terms of advantages of use, modification strategies for improved stability, delivery systems, and clinical applications.

Vaccines are very effective in **preventing illnesses** and **saving lives** [7]. Although traditional vaccines provide **long-lasting protection** against **dangerous diseases**, there are still challenges in developing vaccines for infectious diseases that can evade the **immune system** [8]. Furthermore, **traditional approaches** may not work for **non-infectious diseases** like cancer, so more powerful and adaptable vaccine platforms are necessary [9]. **Nucleic acid-based therapies** have surfaced as a hopeful **substitute** for traditional vaccine methods [9]. In recent years, advances in technology and research investment have made mRNA a promising tool for vaccine development. Compared to traditional vaccine approaches (subunit, killed, live attenuated virus, etc.) used to protect against **hepatitis A, smallpox, HPV** and others; mRNA vaccines have several advantages which are discussed later in the article [9].

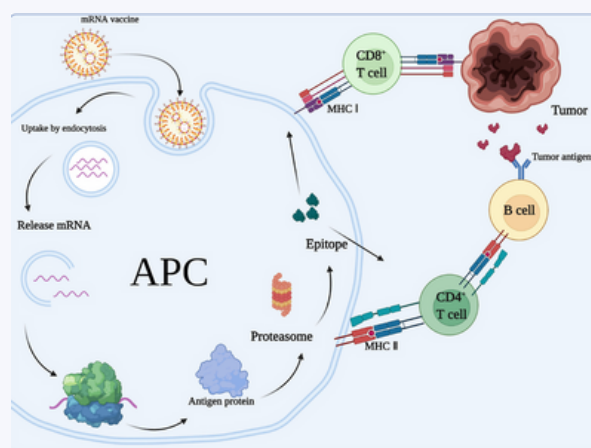## Mechanism of mRNA-based cancer vaccines

mRNA serves as an **intermediate molecule** between protein-encoding DNA in the **cell nucleus** and protein production by **ribosomes** in the cytoplasm, carrying gene sequences in **single-stranded macromolecules** [10]. Non-replicating mRNAs and virus-derived **self-amplifying RNAs** are two types of RNAs currently **under investigation** for use in vaccines [9]. Conventional mRNA vaccines contain the **antigen of interest** and **untranslated regions (UTRs).** In addition to encoding antigens, self-amplifying RNAs also encode **viral replication machinery** that ensures enhanced **intracellular RNA amplification** and **protein production** [9]. In vitro transcription of mRNA can be achieved by using **RNA polymerase** and a **linear DNA template**, resulting in a **synthetic mRNA equivalent** to naturally derived **mature mRNAs** found in eukaryotic systems [11]. Common structures such as a **cap, 5' and 3' UTRs**, **open reading frame** and **poly(A) tail** can also be found on the in-vitro transcribed (IVT) mRNA.

Due to the **rapid degradation** of **naked mRNA** by **RNases** found outside of cells, uptake of **IVT mRNA** is best achieved using **transfection agents** i.e. **(lipid nanoparticles)** that would protect the nucleic acid from extracellular decomposition. **Cellular machinery** commanding the regulation of native mRNA is also utilised in the **regulation and translation** of the IVT mRNA following the successful **cytoplasmic intake** [11].

Pathogen-associated molecular patterns (PAMPs) can be detected by an organism's **innate immune machinery** called **pattern recognition receptors (PRRs)** in case of a pathogen invasion [9]. PRRs are present in **subcellular compartments** as well as extracellularly [12]. Varieties of **intra- and extracellular PRRs** are effective at **recognising** exogenous IVT mRNA molecules, **triggering immunostimulatory pathways** which ultimately result in **inhibited mRNA translation** and subsequent degradation of the molecule [13]. Another important factor when it comes to the **immunostimulatory nature** of mRNA is **contamination** with double-stranded RNA **(dsRNA)** [9]. Contamination occurs during the **in-vitro transcription** and dsRNA is a **potent PAMP**. When recognised by a PRR, **strong type I interferon** production **signal** is elicited which is responsible for a sequence of other reactions that result in translation inhibition and mRNA degradation [9].

This can be regarded as a **negative effect** of the **immunogenicity of IVT mRNA** in the context of **vaccination. Immunogenicity** can be modulated **positively**, too [14]. It includes triggering of adaptive immune response through the **activation** of important **antigen-presenting cells (APCs)** - the **dendritic cells (DCs),** whose maturation is paramount for the immune response from **T and B cells** [9]. Moreover, the addition of adjuvants is believed to increase the **intrinsic mRNA immunogenicity** and **carrier choice** for mRNA vaccines could be **crucial** in facilitating **DC maturation.** The delivery methods relevant to mRNA vaccine use in cancer therapy will be discussed later.

Figure 1. The mechanism of mRNA cancer vaccines [2].

The main purpose of a vaccine is to **introduce antigens** that can stimulate an **immune response** through recognition by immune cells in the body. Herein the mechanism of **mRNA vaccines** specific to cancer treatment is discussed. Upon the injection of the mRNA cancer vaccine, the **exogenous IVT mRNA** and the delivery system components will trigger the recruitment of **innate immune cells** to the site of injection and activation of the host's innate immune response [2, 15]. This leads to the production of **proinflammatory cytokines** and **co-stimulatory molecules**, and subsequent activation of the **adaptive B and T cell responses.** Although the induction of cytokines can improve the effectiveness of vaccines, excessive production of cytokines can lead to various side effects [2]. These side effects may include **autoimmunity** and a reduction in the immune response towards the mRNA vaccines, rendering the cancer vaccines ineffective [2]. Hence, different studies are underway to improve the mRNA vaccine technology to mitigate these issues.

After the uptake of mRNA by the APCs, the IVT mRNA is translated, processed and presented on the cell surface to **trigger** the **adaptive immune response**. Upon activation, the APCs interact with the **T cell receptor (TCR) through the antigen-major histocompatibility complex (MHC) I/II complexes**, leading to **CD4+ and CD8+ T cell activation** and **proliferation** (Figure 1) [2, 15]. Then, the activated CD4+ T cell secrete cytokines such as IL-2 to promote the **amplification** of B cells and CD8+ T cells, thereby enhancing the anti-tumour effect. It then leads to **cytotoxic CD8+ T cell migration** and **infiltration** into the tumour microenvironment, **killing** the tumour cells by the release of **effector molecules** such as **tumour necrosis factor (TNF)** or **granzymes** [2, 15].

Delivery systems for mRNA-based cancer vaccines

There is a **challenging facto**r regarding mRNA vaccines – the nucleic acid molecules are **big in size** and carry a **negative charge** which makes it **unfavourable** for crossing the cell membrane. Apart from the need to **neutralise** their negative charge, the mRNA molecules are exposed to **RNase degradation** outside of the cell [16]. Furthermore, some established methods for **naked mRNA** delivery for vaccination are **unsuitable** for use in humans or are **too expensive** [2]. Therefore, the need for a system that: **A) protects the mRNA molecule from extracellular degradation, B) is effective at crossing the membrane barrier of cells and C) is produced at an affordable cost,** has led to the use of the following delivery methods for cancer therapy with mRNA vaccines [2, 17].

A long-used method for the delivery of genes and nucleic acids is the use of **viral vectors** [16], however, it imposes problems such as **host rejection, immunogenicity**, **toxicity** and even the possibility of **viral genome integration** [16]. Therefore, other non-viral systems have also been explored. **Lipid nanoparticles (LNPs)** are the current delivery vehicle used in the approved **mRNA SARS-CoV-2 vaccines.** This method is the most clinically advanced and has been proven to show effective protection against infection [18]. **Four kinds of lipids** comprise the bilayer of the LNPs (Figure 2) – each lipid has a **distinctive function,** and their proportion is crucial for the effectiveness of the delivery system [2, 17, 19]. The **cholesterol molecules** enhance the **stability** of the **nanoparticles (NPs).**

The phospholipids are important for effective **encapsulation** and **self-assembly** and also aid the **endosome escaping** after **cytosolic intake**. The third important player is the **polyethylene glycol (PEG) modifications** – they prevent the assembly of **particle aggregates** and also provide improvement of **stability** which is important for storing the vaccine. Lastly, **ionisable lipids** are also part of the **lipid bilayer**, forming a complex with mRNA and are responsible for **enhanced intracellular release** due to their ability to gain a positive charge in a low-pH environment. Although LNPs achieve **high efficacy** for **in vivo delivery** of mRNA vaccines, further investigation is needed to confirm the safety and **lack of side effects** [2, 17].

Other groups of **non-viral delivery systems** include polymer nanoparticles (NPs), polypeptide NPs, hybrid NPs and the inorganic NPs - metal nanoparticles [2, 17]. Some of the **favourable characteristics** of these delivery vehicles include **low cytotoxicity**, low cost of production, and **high biocompatibility**, whereas some disadvantages include **lack of solubility** and **inefficient accumulation.**
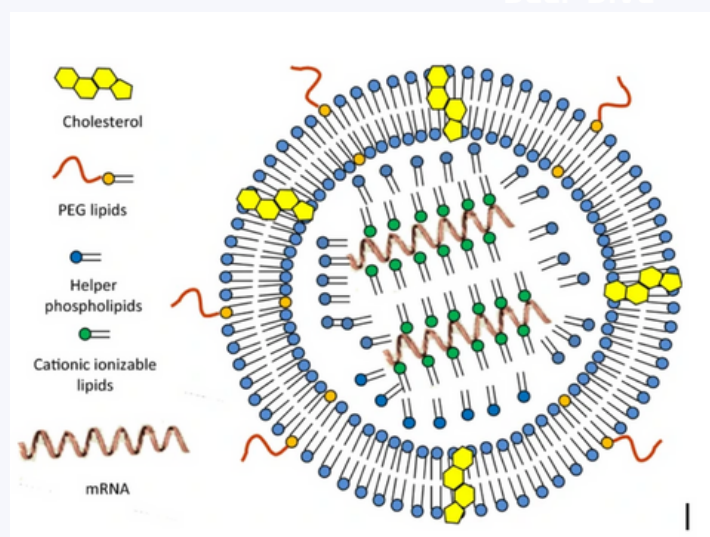
Figure 2. Lipid nanoparticles (LNPs) components. PEG, polyethylene glycol. Adapted from [19].

Strategies to improve the stability of mRNA-based cancer vaccines

As mentioned in the previous section, the **exogenous mRNAs** are often regarded as **PAMPs by the PRRs**, leading to **translation inhibition** and **degradation**. Therefore, modulation of the innate sensing mechanism on exogenous mRNA remains the key consideration when designing **mRNA-based cancer vaccines.** Due to advancements in mRNA research, various strategies have been adopted to modify or **optimise mRNA molecules** to improve transcript stability by **reducing innate sensing**, thereby maximising the **translation efficiency** of exogenous mRNA. Modifications of mRNA vaccines for enhanced antitumor immunity include **5' capping modification**, optimization of **untranslated regions, Poly(A) tail modification**, codon optimization of the open reading frame, nucleoside modification and purification of IVT mRNA to name a few [14].

Advantages of mRNA vaccines over conventional vaccines in cancer treatment

Conventional vaccine treatment usually involves the **stimulation** of the immune system through the introduction of **attenuated pathogens** which the immune system recognises as a foreign particle. However, cancer cells are derived from a patient's own cells and have been **specifically adapted** to evade the immune system, such as by developing the ability to inhibit the production of antibodies against them, rendering cancer treatment by conventional vaccines **ineffective.** On the other hand, mRNA vaccines can be designed to encode **cancer-specific proteins** not normally found on healthy cells, which can be recognised as **foreign particles** by the immune system, and subsequently stimulate an immune response.

In addition, similar to its potential for **rapid response** against emerging infectious diseases, the customizability of mRNA vaccines allows **accelerated development** of vaccines against **emerging strains of cancer.** Other advantageous aspects of these novel vaccine types over conventional ones include **safety, efficacy** and **manufacturing** and **production.** For example, the **non-integrative characteristic** of RNA eliminates the risk of contracting infections, especially for **immunocompromised individuals** [9]. Additionally, mRNA carries the potential to **undergo modifications** which favour their efficacy. Lastly, high reaction yield and simplicity of the process of mRNA production make it ideal for a rapid response towards emerging infectious diseases.

Conclusion

Several aspects need to be taken into consideration in future efforts. For instance, the **clinical translations** of undergoing **preclinical investigations** are largely limited by difficulty in antigen prediction and their **suboptimal immunogenicity** [13]. Furthermore, the **variability** of tumour antigens between individuals could potentially lead to vastly **differential results** amongst individuals. Lastly, multiple dosages with **higher concentrations** than that of **prophylactic vaccines** might be required in the treatment of chronic diseases such as cancer, therefore **high safety standards** are necessary

But perhaps this future is closer than expected. Recently, speakers from the pharmaceutical company **Moderna** (creator of one of the mRNA COVID-19 vaccines) announced the company's expectations to offer mRNA-based treatments to several types of diseases in the span of the **next 10 years** [20]. The spokesperson talked about diseases such as cardiovascular and autoimmune diseases as well as cancer. Currently, the company is in the process of **developing cancer vaccines** targeting different tumour types. During the announcement, the possibility of producing personalised cancer vaccines was also explained in the discussion.

In summary, although mRNA vaccines are a **promising alternative** to cancer treatment, a great deal of research is still required for it to become a reality. Further efforts are required in **developing stable mRNA** with safe and effective in vivo delivery systems. Enhancing vaccine efficacy through addressing the **aforementioned challenges** which are specific to **cancer immunotherapy** must be prioritised before we can expect the successful implementation of this technology in cancer treatment.

References

What is Parkinson's disease?

The Role "Clueless" Parkinson's
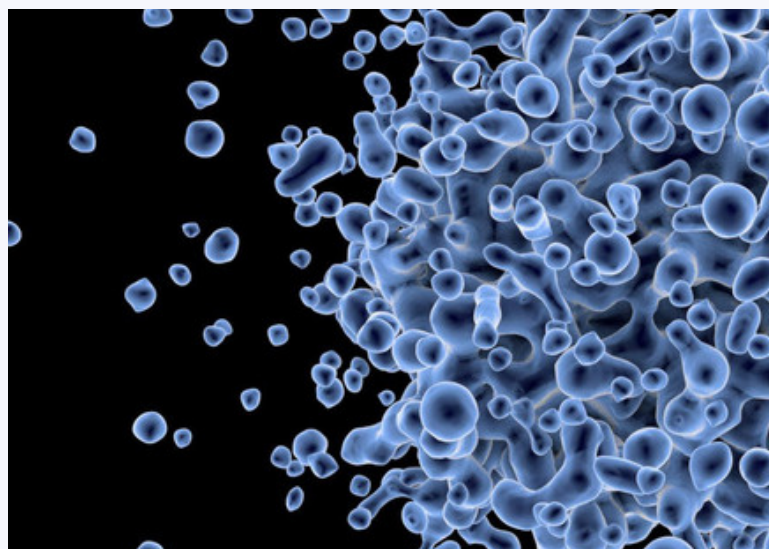
Parkinson's disease (PD) is a **neurodegenerative disorder** categorized by **bradykinesia, tremors, muscle rigidity, changes in speech and postural instability** [1].

The **age onset** of PD is around **60 years**. However 5-10% of patients experience it **before 50 (Young-onset Parkinsons)** [2]. PD is the **second most common neurodegenerative disease**, after Alzheimer's. Global estimates by WHO in 2019 showed over **8.5 million people** in the world affected by PD [3].
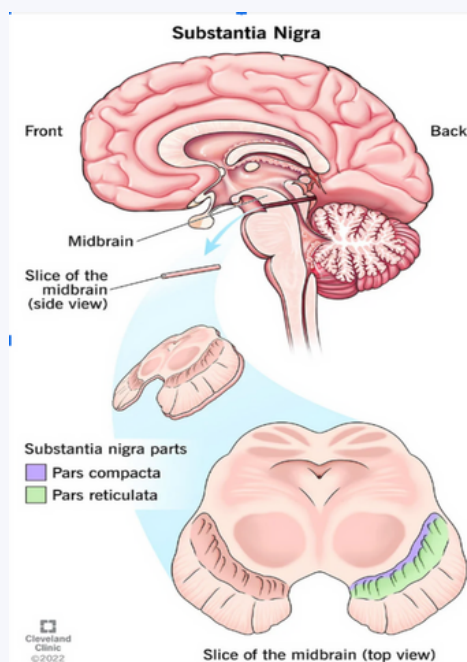
Figure 1. The substantia nigra. The substantia nigra (SN) is located in the **midbrain** and is a part of the basal ganglia. Its function entails **dopamine** production which controls **muscle** movement and tone. The two sections of substantia nigra are SN pars reticulata and SN pars compacta. The former is involved in the **movement** of eyes and the ability to learn and think. The latter is connected to **emotional development**, judgement of risk and reward, motivation and more.

PD is caused by a **loss of nerve cells** in the part of the brain called the **substantia nigra** (shown in Figure 1). These nerve cells release **essential neurotransmitters (dopamine)** that are important for the **control** and **coordination of body movement** [4]. The reason for the loss of nerve cells has been a **highly researched topic.** There is significant progress being made in the identification of genes of interest and the understanding of the **signaling pathways** that could be involved in the pathogenesis of PD.

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## Understanding the genes and cellular pathways involved in PD

There are **many types** of Parkinson's disease, namely- **Idiopathic PD, Familial PD, Young-onset PD, Secondary PD,** and **Drug-induced PD.** Although the **majority** of cases of PD are **Sporadic/Idiopathic,** around 15% of cases account for Familial PD, with 5-10% of patients following a classical **Mendelian inheritance pattern** [5]. Its subtypes- autosomal dominant PD has been associated with a **point mutation** in the **alpha-synuclein gene (SNCA),** causing **intracellular aggregates** of alpha-synuclein (in the form of **Lewy bodies)** whereas, autosomal recessive PD has been linked to **mitochondrial dysfunction** [5].

Autosomal recessive PD- amongst other types of PD- is caused by **mutations** in a set of genes called the **PARK genes** [5]. Mutations in the PARK genes are known to **disrupt** the **electron transport chain**, **protein clearance** (through the **Ubiquitin-Proteasome System** and the **Autophagy-Lysosome pathway**) and **mitochondrial function.** Specifically, autosomal recessive PD has been linked to the **dysregulation** in the function of two major proteins - **PINK1 (PTEN-induced putative kinase 1)** and **Parkin (E3 ubiquitin protein ligase) -** encoded by the **PARK 2 and PARK 6 genes** respectively [5]. PTEN-induced protein kinase 1 (PINK1) is a serine/threonine protein kinase that is a protein kinase localized to the outer membrane of the mitochondria [6]. PINK-1 is responsible for mitochondrial quality management by marking mitochondria for degradation by autophagy through the Ubiquitin-Protease System (UPS). Parkin is an E3 ubiquitin protein ligase that works downstream of PINK1. PINK1 activates Parkin via phosphorylation, and subsequently, Parkin ubiquitinates various proteins on the surface of the mitochondria, marking it for degradation [7].

Apart from PINK1 and Parkin's role in **mitophagy,** they have also been linked to **dysfunction in mitochondrial fission** [8]. Mitochondrial fission is a process involving the **division of mitochondria** to form new ones and it contributes to the **quality control of mitochondria** [9]. In a study conducted by **Poole et. al,** it was found that increased **Dynamin related protein-1 (Drp1)** activity **suppressed** parkin and PINK1 **mutant phenotypes** and on the other hand, **loss-of-function mutations** in Drp1 enhanced parkin and PINK1 mutant phenotypes [8]. Drp1 is a **GTP-ase** that **promotes mitochondrial fission** and is important for **mitochondrial homeostasis**. Even though the full mechanism of action of Drp-1 in regulating mitochondrial fission is still **largely unknown,** these results indicate a likely **genetic interaction** between Drp1 and the PINK1-parkin pathway, and their role in **promoting mitochondrial fission.**
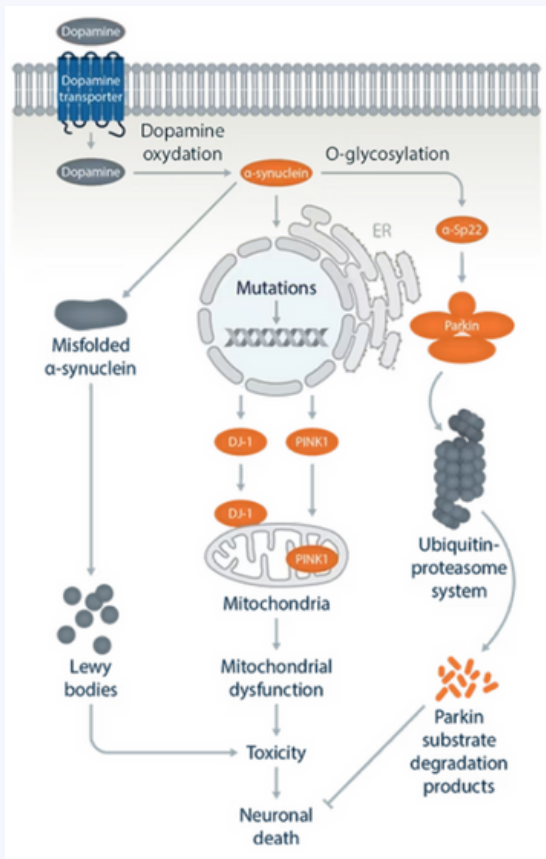
What is the "clueless" gene and how is it significant in context to PD?

In a study conducted by Yang et. al, the relationship between the **"clueless" gene (clu)** in **Drosophila** and **Drp1** was explored. It was found that **clu overexpression** suppressed PINK1 and **parkin null mutant** phenotypes in Drosophila whereas, the **loss-of-function** of clu **intensified** the same. Additionally, overexpression of Drp1 **suppressed tissue damage** and mitochondrial defects in clu **null mutants** in Drosophila. Hence, it was established that clu **regulates** mitochondrial fission by **promoting recruitment** of Drp1 in Drosophila. [9].

Figure 2

These results led to exploring the function of **clu gene's mammalian** ortholog **CLUH (clustered mitochondria homolog).** It was found to regulate mitochondrial fission in mammalian cells. **Overexpression** of Drp1 suppressed the **mitochondrial clustering phenotype** in CLUH knockout cells [9]. Therefore, it was concluded that CLUH complexes with Drp1 and **promotes recruitment** of Drp1 to mitochondrial mammalian cells. Establishing a connection between clu and CLUH with Drp1 marks a significant step in **intertwining them** with the PINK1-parkin pathway, thereby **enhancing** our **comprehension** of PD.

Conclusion

The **growing impact** of PD is evident in **recent statistics**. Current calculations by WHO show that in 2019, PD resulted in an 81% increase, amounting to 5.8 million years of healthy life lost due to disability compared to **2000 figures** [3]. This rise was paralleled by a more than **100% surge** in fatalities, claiming **329,000 lives** [3]. Furthermore, projections indicate an 18% rise in PD prevalence in the UK from 2018 to 2025, with expectations of nearly doubled prevalence and incidence figures by 2065 [11].

This staggering increase in the cases of PD is not only a health concern but also an **economic challenge.** The total cost of PD in the UK has been estimated to be around **449 million to 3.3 billion pounds in annual costs** [12]. These statistics emphasize the importance of the recent discovery of the "clueless" gene which presents a **significant step** toward unraveling the **complexities of PD's causes and pathogenesis.**

References

SUMMER 2023

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D ark matter is as **elusive** and **mysterious** as it sounds. Is it just a convenient solution providing stability for the Standard Model or are we facing an undeniable, new chapter in cosmology? This article aims to briefly outline and evaluate the origins of the dark matter question, the existing theories and practical approaches to its detection, as well as the possible directions this research could take.

Since the 1920s, scientists have theorized the existence of matter **beyond the baryonic kind**, undetectable with the naked eye. The **main evidence** for this was the **bizarre motion** of galaxies and clusters as they spin at rates much **faster than theoretically** allowed. If all the existing mass came from the **visible "classic" matter**, such rotational speeds would have torn them apart ages ago as the **total gravitational attraction** of the system would be too small to counter its **centrifugal force**. As this never happened, physicists inferred that there must be more mass than meets the eye to account for that **extra gravity**, and so dark matter was proposed (CERN, 2020). After considering such cases across the visible cosmos, it has been calculated that this dark matter accounts for **27% of the mass** in the universe, compared to the tiny 5% of baryonic matter - stuff everything we know and see is made of. The other 68% is attributed to dark energy, an **unknown energy** form associated with the **vacuum** of space, and the **accelerating** rate of the **universe's expansion** (Rosenberg, 2019).

Principal Ideas and Challenges

The **main difficulty** in searching for dark matter arises from the fact that it is almost **impossible to detect**. It **interacts** extremely **rarely** with normal matter and solely through the force of gravity. The only effect it has on the universe is expressed through its collective mass which **alters orbits** and **celestial motion.** Since dark matter does not interact with the **electromagnetic force,** it does not absorb, reflect, or emit light (hence the name), which makes most **existing detectors inadequate** for the job (Rosenberg, 2019) .In order to design the right experiments, physicists needed to have a pretty good idea of what they are looking for. **Observations** suggest that a large part of dark matter is **"cold" (CDM)**, that is to say, it travels at **speeds** much **lower** than the **speed of light** and therefore **"clumps"** together. No particles of this kind have ever been detected, but most hypothetical ones fall into this category. **"Hot" dark matter particles (HDM)** are theorized to have a **lower mass** than **CDM** allowing them to travel at **relativistic velocities**, a common **example** is a **neutrino**. A different history of the universe emerges depending on the type of dark matter considered. However, due to these characteristics, predictions based on a primarily HDM universe do not correspond to observations. Their low mass and high speed would mean **structures** forming **very slowly** and **galaxies** emerging **very late** in the universe's history, therefore this **model does not work**. (University of Zurich). Understanding the acceptable range of mass for hypothetical dark matter particles was an essential step towards engineering eligible detectors.

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So far, all research has been focused on "cold" matter, seeing it is more promising. For a long time, the theoretical **Weakly Interacting Massive Particles (WIMPs)** remained the most **favoured candidate** for dark matter. They are **electromagnetically neutral**, **non-baryonic**, and **heavy** enough to have clumped in **density fluctuations** to explain recent cosmological observations. They fit well into the beloved theory of **supersymmetry,** but decades of research using the most sensitive **terrestrial detectors** showed no sign of them.

Although it is too soon to rule out WIMPs entirely, the lack of evidence gave popularity to other theoretical candidates, amongst which are **heavy sterile neutrinos**, **low-mass black holes**, and **axions** (Rosenberg, 2019). Most recently great investments have been made in the latter. Axions weigh much less than WIMPs, but **ignore** the common matter and three out of four fundamental forces the same way. The origins of the axion theory lie in what's called the **Charge Parity problem (CP problem)** in the study of **Quantum Chromodynamics (QCD).** QCD governs the **strong force** and presents a notably **consistent theory** when it comes to experimental data until the issue is noticed. Axions were a result of the **Peccei-Quinn mechanism.** In 1977, **Helen Quinn** and **Roberto Peccei** of **Stanford University dealt** with the CP problem through the idea of **broken symmetries** that a certain **mathematical symmetry** had been broken in the **strong force**, and later research showed that it could be accounted for with a **new particle**. By the 1980s physicists were certain that the **Big Bang** could produce **enough axions** to account for **all of dark matter** (Rosenberg, 2019). The CP violation, referred to as **"the most underrated puzzle in all of physics"** in Wikipedia, arises from the fact that according to QCD, when a particle's charge is **flipped** and viewed in the **mirror** it should no longer obey the same **laws of physics**. Such observations, however, were never made, resulting in the **biggest conundrum** of the **existing particle model**. There are **ongoing debates** regarding the **exact mass of the axion**. We know that the **range** is between a few **meV/c^2 (around one-billionth the mass of the electron)** and **1 μeV/c^2** because if they were any heavier we would have already detected them, and if they were any lighter there would be an excess of them in the universe as the smaller the mass, the greater the resulting mass density. **The Axion Dark Matter Experiment (ADMX)** has been recently **upgraded** and is now at its most sensitive. It relies on axions **decaying** into **microwave photons** for their detection. **Figure 1** is a basic diagram of the **inner workings** of the **ADMX detector**. The **Gen2 version** of it started up in 2016 at the **University of Washington** and now includes the **dilution refrigerator** and has more than **double the data intake rate**. The experiment is **evergrowing** and currently includes scientists and engineers from over ten universities worldwide. The **Large Synoptic Survey Telescope** was launched in 2019 and should be of great help with its large-scale mapping of the universe (Rosenberg, 2019). Both theorists and experimentalists are constantly proposing improvements to the model and its analytical methods but remain ready to be surprised by physics at any moment.

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Black Hole Theories

Another **prevalent theory** is that the **gravitational glue** can be explained by the existence of **mysterious extra-heavy primordial black holes**. In 2015, the **Laser Interferometer Gravitational-wave Observatory (LIGO)** detected a **tiny "chirp"** that was the **first evidence** of **gravitational waves** predicted by **Albert Einstein.** The signal travelled more than a **billion light-years** and was a result of a **powerful black hole merger**. However, after its analysis, it has been revealed that each of the black holes involved must have been at least **30 times heavier than the Sun**, making it three to four times larger than the average. A perplexing question arises from this: these **black holes** are so **heavy** that it seems odd for them to have formed from stars at all, and even if they did somehow form from some **super-massive stars**, their collision or even their being anywhere near each other is **statistically extremely unlikely** within the current age of the universe. The strangest part of **LIGO's findings** was that the signal seemed to **predate** the **formation of stars** altogether.
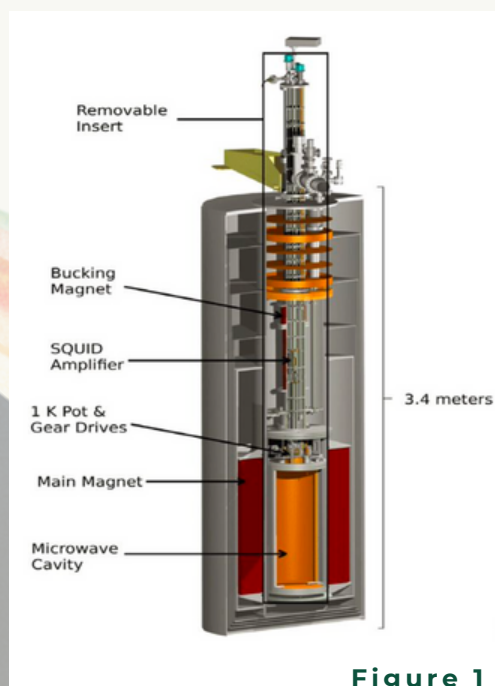

Removable Insert

Bucking Magnet

SQUID Amplifier

1 K Pot & Gear Drives

Main Magnet

Microwave Cavity

3.4 meters

Figure 1

Density fluctuations
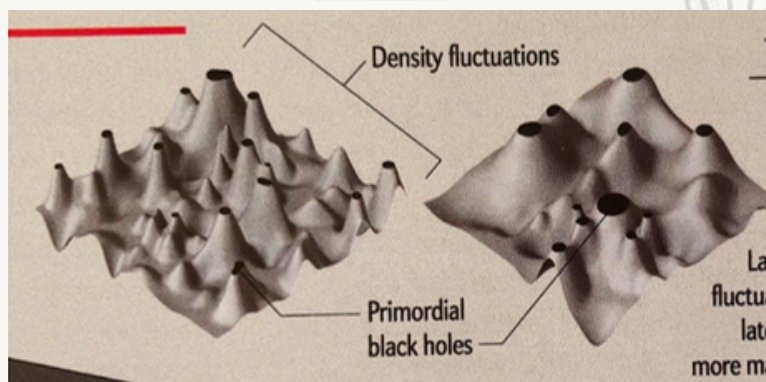
Primordial black holes

Figure 2

Scientists began wondering whether there could be a previously **undiscovered pathway** for **black hole emergence** and whether it could be a potential **explanation** for dark matter (Garcia-Bellido, Clesse, 2019).

In the earliest moments of **cosmic time**, the universe resembled a thick fog of fundamental particles. In the 1970s, theorists including **Stephen Hawking** proposed that certain regions of this fog could **collapse** under their own gravity and form **primordial black holes (PBH)** that shaped the structure of the **expanding space-time** in its earliest stages. As PBHs emit **no light**, they would be very **difficult to detect**, making them one step closer to becoming a **dark matter candidate**. PBHs were formed during the **inflation period (10^{-35}s)** as the rapid expansion amplified **quantum fluctuations** to huge scales.

The larger the fluctuations, the more massive the black holes formed. The model predicts that PBHs were initially formed in clusters due to a range of density fluctuations with **masses ranging** from **100 to 10,000 times** the **mass of the Sun**. Half a million years later this cluster would span **hundreds of light-years** and contain millions of such black holes (Figure 2). As they would collectively grow to feed on gas and dust, they would guide the evolution of galaxies and galactic clusters.

Time

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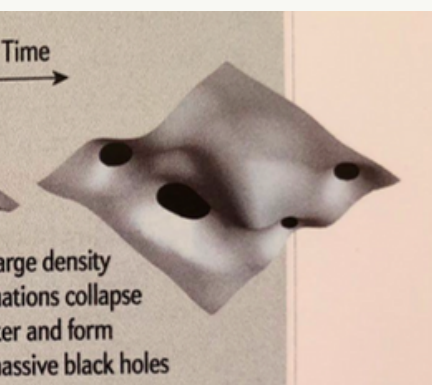
Over time, the numerous PBHs within clusters would collapse to form **massive black holes**. Those that remain, however, orbit massive galaxies and could explain the effects attributed to dark matter. They would also solve the **"missing satellite problem"**, the lack of **dwarf galaxies** that by prediction should have formed around massive galaxies such as the **Milky Way**. In addition, the origin of supermassive black holes could be discovered as PBHs, which could have **seeded** to the formation of the very first **galaxies and quasars**. Now the research is primarily focused on building a reliable database for PBH mergers with the help of LIGO and VIRGO collaborations. (Garcia-Bellido, Clesse, 2019).

Dark Matter or Modified Gravity

Despite several plausible ideas, all experiments so far have failed to produce any real evidence of **dark matter** or **proton decay**. Perhaps the entire approach to this question was conceptually wrong from the beginning, starting with its name, and there is an oddly obvious alternative. What if the **apparent extra gravity** does not come from any **extra mass (or matter)**, but instead is a **consequence of flaws** in the very equations we currently use to describe it? It would require a revision of **Einstein's general relativity** (Hossenfelder, McGaugh, 2019).

The question comes down to this: What if gravity does not always follow the inverse square law? What if there are circumstances under which the classic laws must be changed? In 1983, Mordehai Milgrom proposed the first version of MOND - Modified Newtonian Dynamics. For instance, he speculated that at galactic accelerations below a certain critical point, Newton's laws change to provide a larger acceleration for the same force thus allowing outer stars to circulate faster without any dark matter or extra gravity (Cho, 2017).
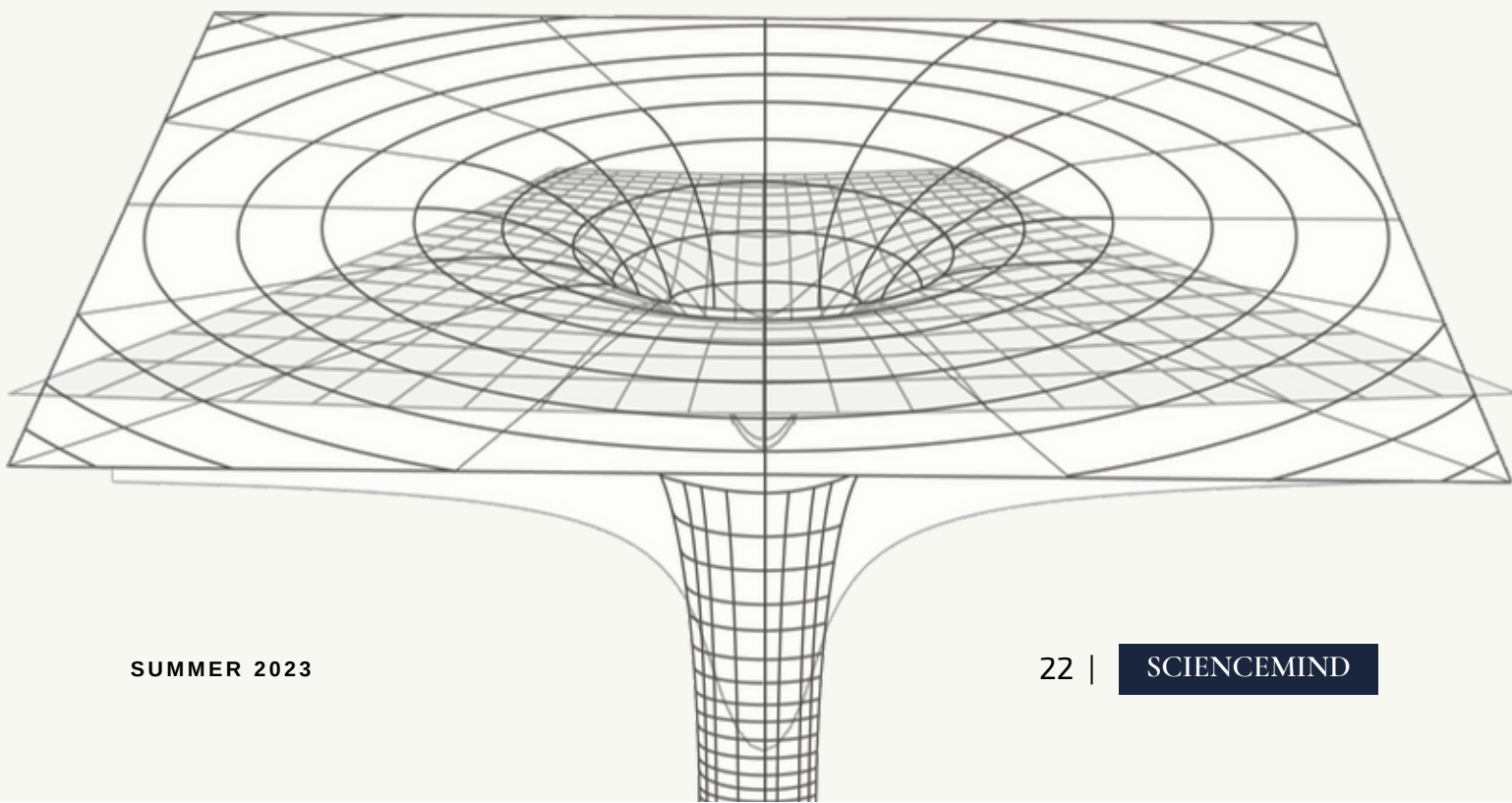
Since then around **ten new theories** arose aiming to incorporate general relativity into the picture as well. All of these new theories look very **unfamiliar** and **mathematically inelegant** by the standards of the **current particle model**, making them **slightly unpopular**. On the other hand, all particle theories have been delivering **null results** since the 1980s and have become increasingly more contrived, slowly switching the focus to other possibilities.

A 2016 study (Figure 3) shows that in a survey of stars and galaxies, the **total gravity** present is **directly proportional** to the amount of **gravity accounted for** by the **visible matter**. If the particle theory of dark matter was true, there would be **no such correlation** as otherwise, it would indicate that the amount of dark matter attributed to a celestial object depends solely on the amount of its visible matter. Since stars and galaxies vary hugely in shape, size, and chemical composition, this assumption is highly implausible.

However, modified gravity perfectly predicts such results. In fact, it predicts many observations that dark matter struggles to explain, for example, the issue regarding the initial rotation speeds of stars. Nevertheless, modified gravity completely ignores the behaviour of the cosmos as a whole (Hossenfelder, McGaugh, 2019).

As research continues, dark matter theories become increasingly oversimplified, flexible, and contrived. Regardless of whether you favour **modified gravity** or **hidden sector particles**, for now, neither provides the promise of a complete picture. Realistically moving forward, the future might require a big step back, a return to the drawing board for reconsideration of fundamental ideas. Maybe the truth is somewhere in between the two concepts, we should find out soon enough.

Figure 3
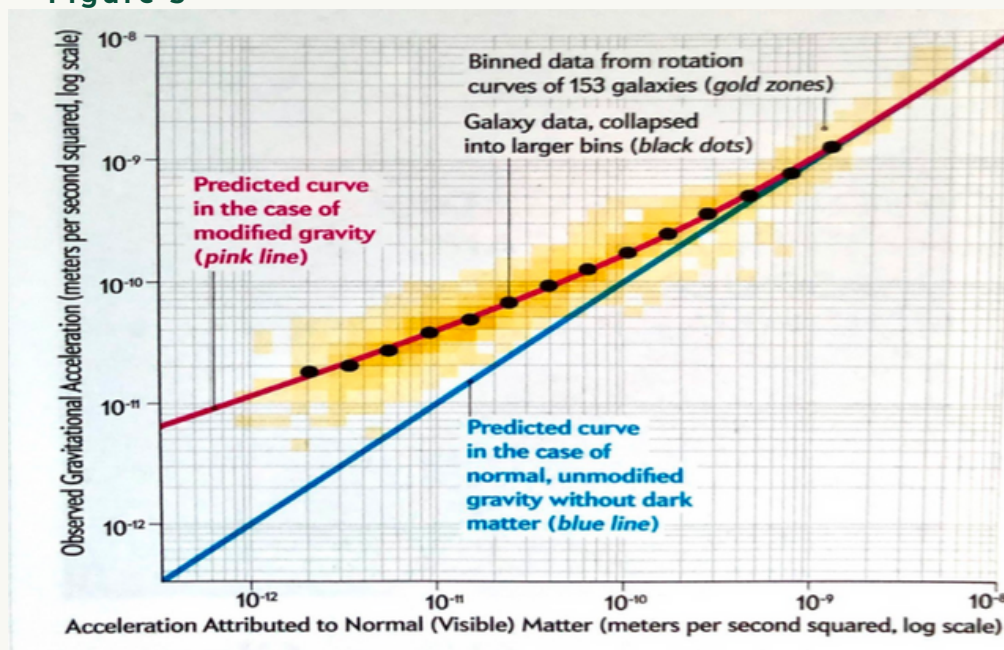
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HUMAN-ROBOT

INTERACTION

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TREADING WATERS

Recently, the portrayal of robots in media has undergone a remarkable transformation, mirroring the shifting attitudes and perceptions towards these artificial creations. Simultaneously, the long-existing field of Human-Robot Interaction (HRI) research has begun to draw as a driving force in shaping the way humans and robots interact. We delve into the evolving relationship between humans and robots by exploring the timeline of media representations, the purpose of HRI research, and the factors that maximize trust in human-robot interactions.

Robots and Artificial Intelligence in Media

Over the past 30 years, the media's portrayal of robots has shifted from primarily mechanical and antagonistic to more intricate, diverse renditions. In the 1990s, iconic robots like Terminator's T-800 cast machines as potential threats to humanity. In tandem, friendly robots like Wall-E and R2-D2 from Star Wars infused robotic characters with a more wholesome and endearing dimension.

The 2000s ushered in an era of diversified robotic roles. Films like "I, Robot" confronted the ethical complexities of human-robot relationships, while "Transformers" introduced robots with cultural legacies and emotions. Fast-forward to the 2010s, and characters such as Baymax from "Big Hero 6" showcased robots' capacity for compassion and caregiving, effectively dismantling the notion of robots as mere tools or foes.

More contemporary media focuses on representations spotlighting emotional connections and collaborations between humans and robots. "Her" unearths romantic bonds between humans and virtual intelligence, while "Ex Machina" navigates the intricate world of human-robot attraction and manipulation world. These evolving portrayals signify a shift in perspective, depicting robots not as mechanical entities, but as prospective comrades, collaborators, and even friends.

The field of HRI research

As media narratives subtly shape public perceptions, the domain of Human-Robot Interaction (HRI) research has taken centre stage, dissecting the practical implications of human-robot relationships. For someone like me with a profound interest in healthcare engineering, HRI stands as a multidisciplinary field, interweaving robotics, psychology, sociology, design, and more with the goal of designing robotics and programming that seamlessly engage with humans across diverse contexts.

This pursuit gains heightened significance against the backdrop of burgeoning social service robots. These entities are meticulously crafted to interact with and aid humans across a gamut of social and service-oriented tasks. Their purpose resonates with enriching human lives. From Elderly care and Healthcare to Education and Disaster Relief, social service robots assume an ever-expanding role. Consider Pepper by Softbank Robotics—a robot designed to perceive emotions. In terms of Education, we have recently witnessed the emergence of Delle, a robotic Dolphin, heralding a potentially humane alternative to traditional zoos.

At its core, HRI aspires to bridge the divide between technological capability and human expectation. This field seeks to nurture robots that aren't just user-friendly and efficient but can appropriately respond to human emotion with some level of emotional intelligence. By unravelling the intricacies of human psychology and the subtleties of social dynamics, HRI research clears the path for the seamless assimilation of robots into human environments.

Culture and the "Uncanny Valley"

Within human-robot interactions, trust serves as the cornerstone of successful collaboration. Studies surrounding the exploration of trust dynamics in human-robot interactions suggest that trust is a lynchpin that determines the effectiveness of interactions and the willingness of humans to rely on robots for various tasks.

However, indications of "trustworthiness" are extremely subjective.

Each culture infuses its distinctive language, tone, and gestures, altering how humans engage with robots. This cultural undercurrent also extends to proxemics, the spatial relationships between individuals, where differences in what we consider our own personal space can impact human-robot interactions.

The Uncanny Valley theory posits that as robots resemble humans more closely, comfort increases until a tipping point, beyond which discomfort takes over. This theory underscores the challenge of striking a balance between human likeness and a sense of eeriness in robot design.

Cultural variance adds layers to this challenge. Preferences for humanoid or machine-like robots differ across cultures, yet consensus emerges that humanoid robots suit human-like services. Ensuring their design elicits comfort while avoiding the eerie Uncanny Valley is a delicate art.

Sprout

I had the privilege of speaking with Jeffrey Chong and Theodore Lamarche, two of the engineering students who worked on Sprout, a remarkable soft robot AI, which is currently on exhibition at Science Gallery London. Jeff, a recent graduate, and Theo, a third-year electrical engineering student, collaborated on Sprout as part of their final project and dissertation, respectively.

Sprout itself is a collaboration between Air Giants, a Bristol-based robotics company and Dr Oya Celiktutan, an Associate Professor of Robotics at KCL.

Jeff and Theo revealed that Sprout was envisioned as an interactive exhibition, a creation that beckons users to engage with it and, intriguingly, carries an inherent desire to interact in return. "We went in not really knowing," Jeff shared, reflecting on their expectations at the project's inception. Sprout's essence rested on fostering a palpable sense of friendliness—an amalgamation of meticulous research and intuitive design.

Considerable focus was directed toward how Sprout was perceived by onlookers and its connection to friendliness. Inspiration was drawn from diverse sources, and the unique shape of Sprout, Theo emphasized, was influenced by studies of octopi and their reactions to human presence, aligning its form with organic curiosity. This link also allowed the team to make use of octopi behavioural research to create parallels between human interpretation of octopi movement to that of Sprout. Jeff cited a Heider and Simmel study as a major inspiration, fascinated by the human ability to interpret expression even after several layers of abstraction.

As we discussed further the details of Sprout's function, Jeff and Theo emphasized the confluence of visual data and motion capture. The dynamic interplay between movement, emotion, and perception came to the forefront.

Theo emphasized the collection of skeletal data, capturing the velocity and body movement of those within Sprout's enclosure. "In the day-to-day, Sprout isn't learning," he noted, stressing the significance of interpreting ongoing interactions. He mentioned that the hope was to implement more machine-learning aspects into Sprout's programming as the project continued on.

However, the implementation of machine learning into Sprout's programming is not without risks. Jeff voiced concerns about behavioural convergence and the potential pitfalls of constant machine learning. Behavioural convergence refers to the algorithm settling into a constant state, regardless of the state of the input, which, in Sprout's case, would lead to a complete loss of responsiveness. Balancing dynamic, fluid motion with controlled repetition posed a conundrum when combined with the unpredictability of a version of Sprout, whether fully or partially influenced by machine learning.

Theo reflected on the importance of fluidity to make the robot appear less robotic, a strategic choice made easier by the fabric-based aspect of the robots construction, in fostering a deeper human connection.

Ethical considerations also played a pivotal role in shaping Sprout's journey. As Sprout was intended from the beginning to be available to the public, the team was required to navigate a landscape where media and public exposure necessitated re-evaluation and resubmission to an ethics committee. Striving for privacy and anonymity, they stressed that Sprout's data was meticulously anonymized, ensuring that visual information never left the confines of the camera.

The conversation then gravitated towards Sprout's behaviours, focusing on the intention behind its actions. They addressed the fascinating paradox that many individuals don't perceive Sprout as a robot at all.

Theo highlighted their commitment to positivity, emphasizing Sprout's role as an exhibit that invokes happiness and curiosity. The deliberate avoidance of negative behaviours was a conscious choice, rooted in the intention to foster playfulness rather than negativity. The aim was for all of Sprout's behaviours to either be explicitly positive or neutral, any negative impressions would be left entirely to the human's interpretation.

Jeff and Theo delved into the intriguing interplay between Sprout's creation and the myriad of human responses it elicited. They discussed how Sprout's ability to engage was the most important aspect of its interactions. The basis of the research is more focused on the human response to Sprout as opposed to any software aspect. They discussed managing the balance between keeping Sprout responsive and ensuring that interactions are genuine to the approach of the human. "Sprout does not coddle", Theo remarked, further elaborating that Sprout has been designed to respond in kind to those who interact with him more enthusiastically.

The two expressed enjoyment in the opportunity to craft interactions that genuinely captivate individuals. Jeff introduced the concept of a "reverse Turing test," to describe Sprout, where people are aware of the robot's identity, yet repeatedly the attempt to evoke a human-like response persists.

Our conversation culminated with Jeff and Theo making a request to all those who may visit Sprout to " Just go for it!", encouraging any visitors to be bold and playful when interacting with Sprout.

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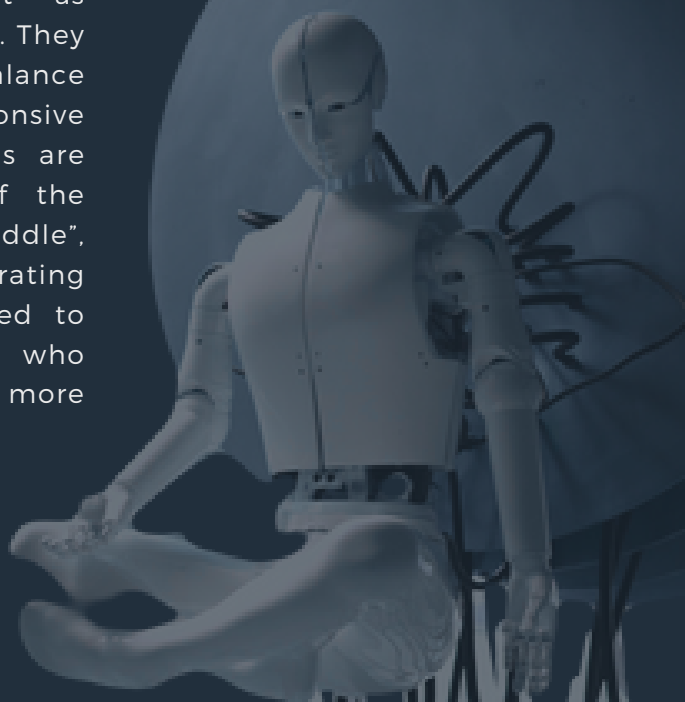
# Proton tunneling effects in biological systems

DEEP DIVE

WRITTEN BY SAMUEL GINZBURG
EDITED & DESIGNED BY OLIVERA MITEVSKA

Recent advancements in proton tunneling

Quantum biology is a new emerging field focusing on the non-trivial features of quantum mechanics (including quantum coherence, quantum tunneling, superposition and quantum entanglement). Since the discovery of DNA by Franklin, Watson, Crick, and Wilkins in 1953, it has been proposed that a double proton transfer tautomerization mechanism in the DNA could produce stable errors in the genetic code. Where, the two isomeric compounds (tautomers) can rapidly interconvert by reversible chemical reactions. The quantum tunnelling of the protons through an energy potential barrier separating the nucleotide base pairs on the two strands of DNA has been predicted to significantly contribute to this mechanism, which makes it particularly intriguing. Each base transforms from its standard canonical form to its tautomeric

form when the H-bond protons move from a base site on one strand to the corresponding site on the other strand. Each strand of DNA could pass through the DNA replication machinery (the replisome), where the tautomeric form of the base is mismatched with the incorrect corresponding base on the copied strand. However, this is on the condition that tautomeric pairs can survive the DNA cleavage process in the helicase. It has been recently found using NMR-relaxed dispersion methods that G-T mismatch pairs are present in the B-type DNA duplex (The most common and stable form of DNA found under normal psychological salt concentrations and neutral pH) with a suggestion of tautomerization (Figure 1) between G-T* and G*-T base pairs (asterisk represents the specific tautomeric form of the base, enol).
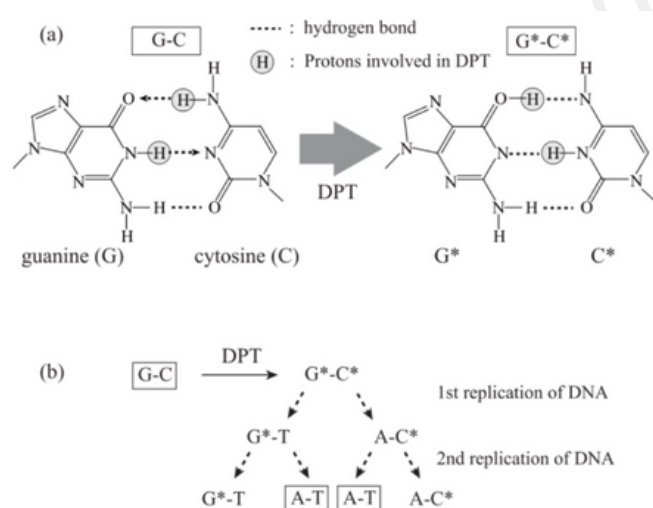
In a recent study by Slocombe et al. (2022), the researchers argued the nature of the double proton mechanism and demonstrated a more accurate process. In fact, the periods of the tautomeric states do not significantly affect the probability of a base pair mismatch since the double proton transfer process occurs so quickly in comparison to biologically relevant timescales (on the femtosecond time scale). Considering the proportion of tautomeric base pairs to canonical base pairs present at


Figure 1. A pictorial model where a G-C base pair mutates to an A-T base pair via a G*-T and an A-C* mispair. (a) A scheme for G-C and G*-C* base pairs tautomerization. The tautomerization is a result of the double proton transfer mechanism in the base pairs. (b) A scheme for G-C base pair mutation to an A-T base pair via a G*-T and a A-C* mispair.

chemical equilibrium is more important. The study involved the open quantum system (OQS) method to model the proton dynamics (The quantum mechanical system interacts with an external quantum environment) to account for the internal energy increase of the system and/or to heat transfer to the surroundings (dissipation effects). The lifetime of the tautomeric states was estimated using the potential energy surface (PES) for the double proton transfer reaction via a back-to-back double Morse potential. Therefore, the parameters of the potential made it possible to calculate the quantum tunnelling correction and estimate the lifetime of the tautomeric state. The first figure demonstrates the proton transfer reaction potential energy landscape of the double H-bond between the C and G bases. The tautomeric state is rarely populated due to the high energy-forward reaction barrier.

Interestingly, the determination of the lifetime of tautomeric species is crucial for understanding their effect in quantum biology. Monitoring the flux probability changes between the left and right hand potential well allowed to estimate the quantum contribution, KQM. The calculated tunnelling factor, was very large (~105), suggesting a non-trivial quantum contribution to the reaction rate where the system readily interconverts between the canonical and tautomeric forms via quantum effects. In comparison, purely classical calculations, suggest that the tautomer is classically unstable due to the

relatively low reverse reaction potential barrier. Surprisingly, the used model predicted a higher rate of tautomerization than the overall rate of sponta-neous mutations (~10-8). However, there is consistency between the model and the efficient DNA repair mechanism.

Other research groups evaluated different models to estimate the tunneling factor using an imaginary frequency in the transition state (TS). However, the derived Wigner tunnelling factor wasn't appropriate if the intrinsic reaction coordinates (IRCs) shape is asymmetric or if its imaginary frequency is large. To calculate the tunneling factor, a transmission probability (TP) for the potential needs to be analytically obtained using fitting parameters to fit the potential. A common way to calculate TP includes using the WKB approximation, where the wave function is
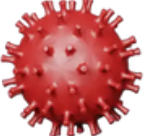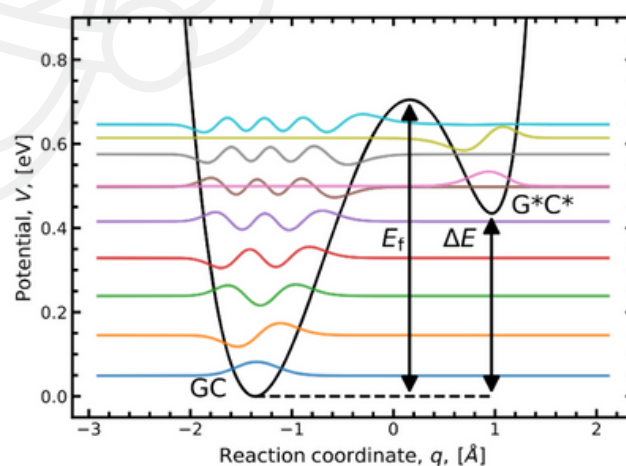

Figure 2. The potential energy landscape of proton transfer reaction. The first ten energy eigenvalues (eigenstates) for a single proton are depicted horizontally by colored lines. The forward barrier is characterized by 0.705 eV, a reverse barrier of = 0.270 eV and a reaction asymmetry between the canonical and tautomeric form of = 0.435 eV. The potential was modelled using the quantum Brownian motion model, where the defined quantum system (a proton in the double well potential) interacts
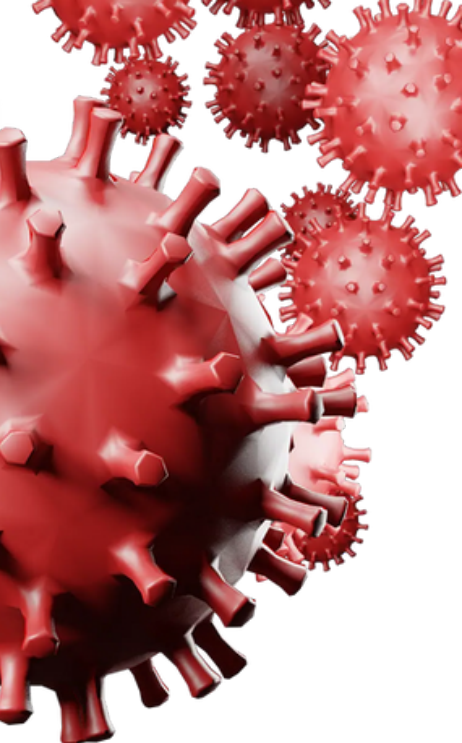
assumed to be an exponential functional form with a slowly varying amplitude and phase with position, as used in semiclassical calculations. However, the approximation introduces two major issues: (1) Calculation errors near the top of the potential barriers and (2) possible errors within the energy region above the top of the barrier. Hence, a more advanced approach can be used that has been quite intensively implemented in the modelling field of semiconductor and optoelectronic materials for solving the one-dimensional Schrodinger equation, i.e., the transfer matrix method (TM). In this method, the wavefunction at each point decomposed into two complex numbers, called wave components. These components can be used to construct a transfer matrix. The advantage of the method is that it allowed the precise calculation of TP values for arbitrary potential barriers using the Eckart potential modelled as a G-C pair.

Applications to the study of binding proteins

Quantum tunneling presents a variety of potential in the context of studying molecular receptor recognition and binding to contribute for better medical intervention and mechanistic understanding, as seen in the spike protein SARS-CoV-2. It is building the possibility that the lock and key, or shape-based mechanism used to describe enzymatic pathways and mechanisms, might be replaced or modified by a quantum tunnelling mechanism. From the biomedical perspective, the mentioned quantum studies directly link biological receptor mechanisms. An important class of cellular receptors includes the G-protein coupled receptors (GPCR). Mechanistically, the receptor is activated by an incoming extracellular signal, in which GTP binds to the activated G protein and dissociates into two subunits. After GTP hydrolysis, the G-protein reassembles and is available again. Additionally, these binding receptors can bind neurotransmitters to open ion channels, and more interestingly, they are evolutionarily related to the retinal photoreceptor protein rhodopsin. Rhodopsin consists of the light-sensitive chromophore retinal in an opsin protein, with the chromophores being crucified significantly concerning quantum

coherence effects in energy and charge transfer. The coupling of vibrational to electronic states is mainly imagined in proteins in which the chromophore is embedded. However, it is still debatable whether GPCRs operate through a mechanism related to electron transfer. More recently, attempts have been made to apply the vibrational theory of olfaction in a different physiological context: the binding of neurotransmitters.

Intriguingly, GPCRs seem to play a role in the disease associated with SARS-CoV-2 infection. Recent studies modelled the interactions between the spike proteins and the ACE2 receptor that modulates the form of the GPCR-binding ligand angiotensin as a vibration-assisted electron transfer. An OQS approach was used to model the interactions of a biological system with their environment. The receptor was modelled as a dimer, and the representation of vibration-assisted tunneling in the context of SARS-COV-2 is shown in Figure 3.
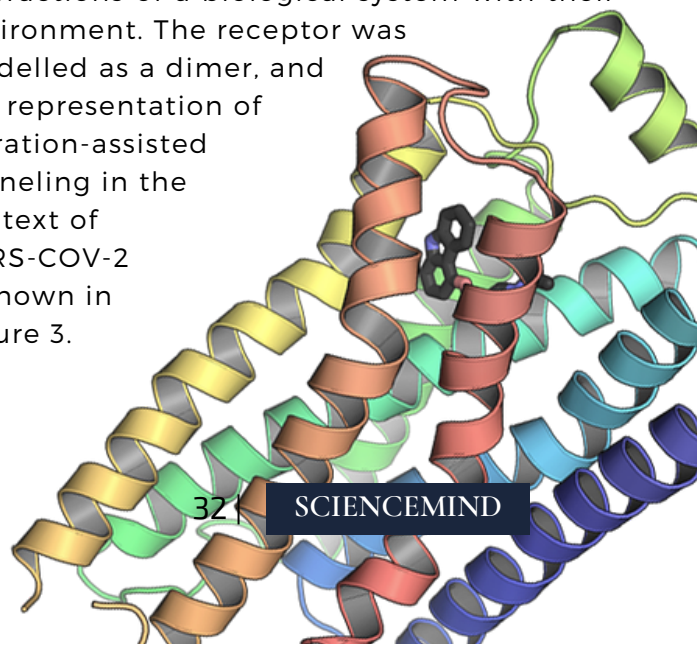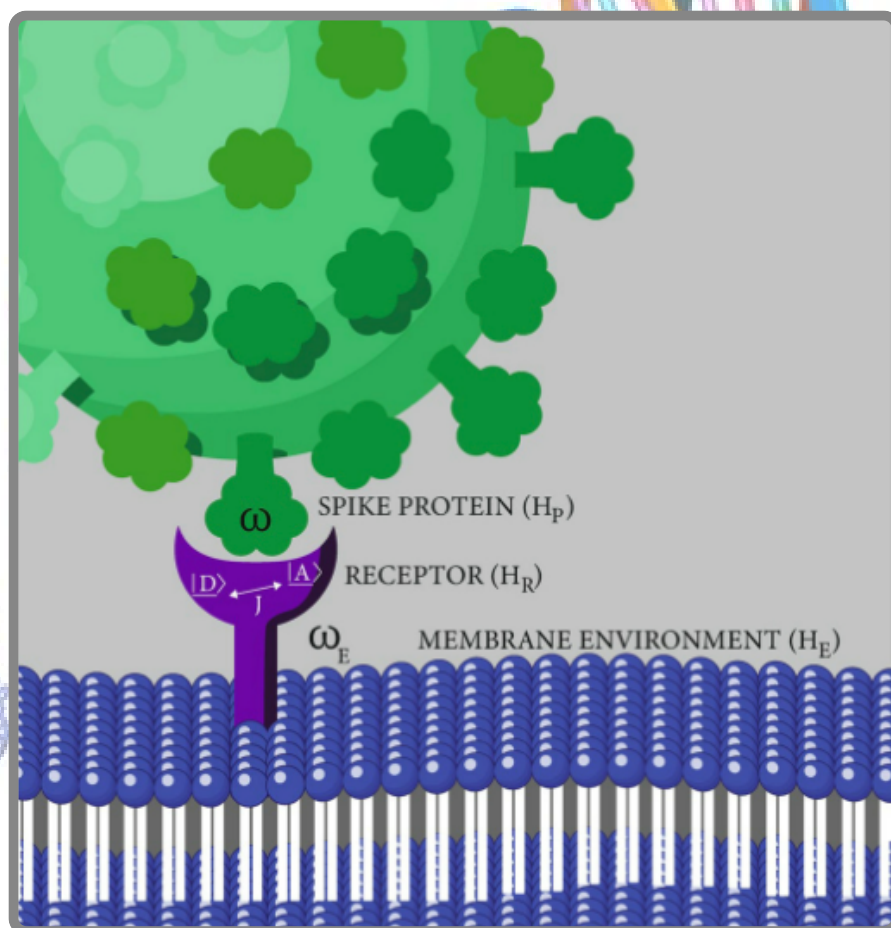
Figure 3. A pictorial illustration of vibration-assisted tunneling as seen in the spike protein. The spike protein vibrational spectra match the energy of transition for an electron in the ACE2 receptor, facilitating electron transfer and the activation of the receptor. where εD and εA are the energy levels of the donor (D) and acceptor (A) levels, and J describes the coupling between levels and the likelihood of transition with associated frequency ω

Results show that there exists a specific parameter range in which vibronic modes enhance electron transfer, with this effect becoming more pronounced as the coupling strength between levels increases. However, when the coupling is either too weak or too strong, the vibronic mode has no beneficial effect or even hinders electron transfer. Essentially, the stronger the connection between these energy levels, the more significant the role vibronic modes play in promoting electron transfer. The study highlights a biologically relevant parameter window where vibration-assisted tunnelling plays a significant role, with different vibronic frequencies showing similar effects but with varying parameter regimes of enhancement. This implies that vibronic modes can have a consistent role in facilitating electron transfer in biological systems, but the effectiveness of this role may vary depending on the specific conditions and frequencies involved.

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The Emergence of Eusociality

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EDITED BY NIKITA KATHURIA
DESIGNED BY YUSRA-AINA CHOUDHURY

SHALLOW DIVE

Sometimes we encounter systems whose elements are so seamlessly integrated that it is impossible to pick them apart and find out how they were created. Often because they have perfected themselves over very long periods of time. For instance cells: A cell is a system made of components such as mitochondria, chloroplasts and endoplasmic reticulum. Since prokaryotic cells have been known to exist for at **least 3.4 billion years**, it is too late for us to be able to point at the environmental demands that caused their components to begin to work together.

However, **bees and hymenoptera** (which include wasps, ants and termites) - due to their relatively recent evolution **(100 million years ago)** give us a unique window to pick apart the components of their cooperation. **Bee societies** are puzzlingly complex. They are democratic, hierarchical structures with a **queen** who is the mother of every other bee in the hive. All other females in the hive - called **worker bees** - are born sterile except in the absence of the queen when they can give birth to male drones. This phenomenon brings up a fundamentally subversive challenge to explain why in a world fraught with struggles among individuals to spread their genes, did worker bees give up their reproductive rights? Which evolutionary pressures can explain this submissiveness which Charles Darwin called the sterile worker bees his one special difficulty?

For a long time, many scientists believed that the solution to this paradox lay in the **kinship theory** also known as the inclusive fitness theory, first proposed by sociobiologist **W. D Hamilton in 1964**. According to the theory, instead of the survival of individual organisms or an entire species, it is the multiplication of genes that is at the heart of natural selection. Hamilton introduced the concept of relatedness or 'r' - a measure of genetic closeness to make sense of social behaviour.

If X and Y share an 'r' value of ¾ or have ¾ genes in common and Y and Z share an 'r' value of ½ or have ½ genes in common

Then X and Y are more closely related to each other than Y and Z.

He claimed that Y would rather be more altruistic towards X than Z because X's survival would ensure the survival of more of Y's genes.

A Tool to Make Sense of Social Bee-haviour

The theory established relatedness and the drive for maximum genes to be passed on to be a reason for sociality and predicted that altruistic and social behaviour is conducted after a subconscious calculation of the risks and benefits to the individuals involved. He summarised his theory **using the Hamilton's rule** which he expressed as an equation ($r \times B > \mathbb{C}$) where B and $\mathbb{C}$ are the benefits (in number of offspring equivalents) and costs (in number of offspring equivalents) to the individual respectively.

This **gene-centric approach** to altruism in nature captured the imaginations of many academics especially after **Richard Dawkins** published his book, the **'The Selfish Gene' in 1976**.

Coming back to the bees and other hymenoptera , their societies are often termed as eusocial. **Eusociality** is a form of social organisation in which organisms reduce their own reproductive potential to help raise the offspring of others. Bees are highly eusocial. In a hive of **20,000 bees**, only one bee - the queen - produces offspring, the other bees: the workers and the drones do not contribute any offspring in the hive. The worker bees produce honey, keep the queen clean and fed, and rear her eggs.

Monogamy in Hymenoptera societies

To put relatedness among worker bees into context, bees follow the **haplodiploid method** of sex determination. The queen takes one or more mating flights during which she leaves the hive and mates with drones of other hives. She is able to store their sperm and fly it back to the hive. Females are born from eggs which are fertilised inside the queen while males emerge from unfertilised eggs.

If all bees had the same father, they would have ¾ of their genes in common, higher than the ½ value shared by parents and offspring. This may have incentivised workers to care for their siblings instead of giving birth.

It was well known that monogamy maximised relatedness and so to support the kinship theory, in **2008** scientists investigated and found that the ancestors of all the **hymenoptera lineages** they studied **practised monogamy**.

A study also investigated the queen-making behaviours of worker bees, suggesting they were motivated by relatedness.

When I first set out to write this article I too believed that the kinship theory was correct but after a little investigation, I found that science now offered an alternative .

The Alternate Hypothesis

In **2010**, an article published in the journal **Science by Martin A. Nowa**k and his colleagues claimed that the kinship theory and by extension, the haplodiploidy hypothesis was unnecessary and could not be applied to ecological situations as a predictor of behaviour. Additionally, the empirical data obtained by using the kinship theory was a result of confirmatory bias.

They claimed that the conditions imposed upon the variables in the calculations using the kinship theory were extremely stringent thus, the derived values could not be accurately applied to real-life, contesting that high relatedness within eusocial orders is a consequence rather than a cause of eusociality. In addition, a termite species -**Zootermopsis angusticollis** -has been found to establish eusocial groups with central monarchs

through combat among strangers rather than through measures of relatedness. Nowak and his colleagues offered a more story-like origin of eusociality. They outlined **5 stages**:

1. During the first stage, a small group within a population **came together**, probably to have a defensible nest or perhaps due to synergism or manipulation between unrelated individuals.
2. In the next stage, group dynamics got **consolidated**. This is when the propensity of bees to work together kicked in. For example, when a bee senses another bee doing a task, it moves on to find other work. Bees also know how to resume an incomplete task. These sensibilities have been found in social as well as solitary bees. In an experiment, solitary bees were forced into an artificial social environment where they began to cooperate and divide labour, suggesting that some cooperative traits were pre-existent.

The division of labour in a hive is explained by the **fixed-threshold hypothesis**. The theory posits that depending on their genotype, bees have varying levels of response thresholds. When two bees are offered the same task, the bee with a lower threshold will submit to doing it while the other will move on. These tendencies (called pre-adaptations) are likely not a deliberate stroke towards eusociality.

3. Next was the origin of eusocial alleles by **mutation or recombination**. While this may sound improbable, there are two confirmed examples of this - in primitive ants and Solenopsis invicta (fire ants.)

For instance, the transition from regular ants to the wingless labour caste took place 110 million years ago when there was a change in the network of genes that controlled wing development, causing it to turn off in the presence of certain environmental factors such as dietary intake. A similar phenomenon is observed in the queen-making process where any larvae who are fed 'royal jelly' by worker bees can become queen due to its high nutritional value that stimulates ovarian development.

The fourth and fifth stages, while not studied extensively, are thought to be the **emergence of traits** favoured by the selection pressures in the new environment leading to selection within the colony and the emergence of the worker and the drone caste.

Back to Kinship
In **2018** a group of scientists introduced the possibility of 'bet hedging' to the evolutionary school of thought. Bet hedging is a risk management strategy often used in bettings and insurance. When factored into Hamilton's equation, it refines it to involve the unpredictability of ecological factors into its calculations.

Their key insight was that in times of changing climates and food insecurity, individuals strive towards a consistent number of offspring. Since they are not competing with each other to bear more offspring, they use their resources to 'hedge their bets' as in, behave altruistically towards other individuals to ensure that at least some of their genes (common genes) are passed onto the next generation.

Conclusion
While the emergence of eusociality still does not have a conclusive theory, it remains a captivating area of study in evolutionary biology. The ability of certain species to develop **highly complex social structures**, featuring cooperative care and reproductive division of labour has been a driving force behind their ecological success. We have **2 strong** contesting theories. I hope we can expect further investigations from both perspectives, so the scientific community can adopt a collective stance.

References

SUPERSONIC FUTURE
Or how to get from London to New York in 3 hours

In 2003 the first-ever supersonic jetliner, Concorde, completed its last flight. This marvel of 20th-century aviation was a French-British venture that had served the wealthy and adventurous of the Global West since 1976. Reaching twice the speed of sound at Mach 2.04 (Mach meaning multiple of the speed of sound), it cut transatlantic flight times in half with an Olympus 593 engine that guzzled a monstrous 25,629 litres of fuel per hour. It was extremely demanding, over a million champagne bottles were consumed onboard, and the ticket prices rose to $6,000 on a one-way journey. Nevertheless, the feat of engineering was retired with bittersweet sentiments, described as a technology ahead of its time. It was massively fuel inefficient, expensive to maintain and, importantly, limited to transoceanic routes due to its deafening, glass-shattering, plaster-cracking sonic booms that propagated to 7,200 km over land, resulting in most countries banning Concordes from their airspace [3].

Twenty years later, though our world seems most interconnected and fast-paced, the word "supersonic" is associated more with a deadly missile than a luxury trip. According to the US Federal Aviation Administration, general aviation passengers complete 25,506,000 flight hours a year, a time period larger than the one between the modern day and the foundation of the Roman Empire [2]. In an era so reliant on dynamic global cooperation, why has no one tried to reintroduce commercial supersonic flight? Since the Concorde retired, we have sent 5 rovers to Mars, landed on shooting comets, sampled solar winds, discovered exoplanets, had a probe reach interstellar space, landed on the dark side of the Moon and launched over 400 humans into space.Yet, New York to London is still, on average, 7 hours of leg cramps and insomnia with a direct flight.

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EDITED BY ZETA IOANNOU
DESIGNED BY YASMIN MARZIAKHALL

The answer is rather obvious - it is not easy to fix everything that was wrong with the Concorde. Building a supersonic jet in itself is no longer a breakthrough, but facilitating widespread supersonic air travel in an economically and environmentally sustainable manner, would be a dramatic one. The good news is that scientists and engineers have not abandoned supersonic vision - and there is increasing hope on the horizon.

Key Players

Perhaps surprisingly, none of the aviation giants are designing a Concorde 2.0 in-house. Companies like Airbus, Rolls-Royce, Boeing and Embraer all act as large sponsors and manufacturing partners for a handful of new, emerging startups [1]. Over a dozen active companies are working on their own versions of a new commercial supersonic plane, with Hermeus even aiming for a hypersonic craft (specifically Mach 5, aka 5 times the speed of sound!). Notably, the leading player in the supersonic race is the Colorado-born Boom Technologies and their Overture, a supersonic passenger airliner. While most companies pursue a simpler goal of building a private jet, Boom wants to see its technology spread publicly. With support and funding from NASA, the US Air Force, United Airlines, American Airlines and many other prominent names, Overture, the first supersonic passenger craft since the Concorde, is set to take to the skies by 2027 at 1.7 Mach speed, 100% Sustainable Aviation Fuel, 7867 km range on 600+ routes carrying up to 80 passengers.Importantly, Overture will fly over land as well as water.

**Boom Technology Overture aircraft.
Image Credits: @boomsupersonic on
Instagram**

This is one of the key differences with the Concorde that give Overture a chance at long-term success. Over 130 planes have already been ordered for giants like American Airlines, United Airlines, Virgin Atlantic and Japan Airlines [3]. The design also carries some improvements, such as the modified delta planform and gull wings, which minimise drag (and hence required engine thrust), as well as enhance supersonic performance and subsonic stability, making the aircraft safe and efficient. It is set to be twice as fast over water and 20% faster over land compared to conventional aeroplanes [8]. Other notable competitors in the supersonic market include the Nevada-based Aerion and Boston-based Spike Aerospace. Both aim to create a supersonic private jet by the end of the decade [9]. Remarkably, Spike is designing a windowless aircraft in an attempt to reduce overall weight (which reduces fuel consumption and simplifies manufacturing) by fitting the cabin with Multiplex Digital panoramic screen systems that display the outside in HD [6].

It is also worth mentioning that Russia and Japan have been working on unnamed supersonic jet projects for some time, but the details are kept confidential and the intended purpose of the technology remains a mystery.

Taming the Boom

Sonic booms are thunder-like sounds that people on the ground hear when a supersonic aircraft flies overhead. As the aircraft flies through the air, it pushes air out of its way, continuously creating sound waves. These sound waves, or air pressure waves, move away from the aircraft in all directions at the speed of sound. The air pressure waves pile up ahead of the aeroplane and get compressed, forming shockwaves. The shockwaves move out and away, creating a sudden change in pressure. When the energy from the shockwaves reaches our ear, it is heard as a loud crack of a sonic boom [4].

Thanks in large part to the efforts of NASA Aero with Lockheed Martin, we are looking at the prospect of crossing the sound barrier without potentially causing hearing impairments or the shattering of glass. Along the way, researchers turned their attention to the idea of lowering the intensity of the sonic booms to a "thump", claiming it will be "as loud as a car door closing", according to NASA [5]. In other words reducing the sharpness of the curve produced by the sound waves by manipulating the shape of the aeroplane. Its upcoming X-59 jet (of the Quesst Project) is set to fly this year over several USA towns and cities to gather data on human responses to the sounds generated by supersonic phenomena [5].

True future prospects

As exciting and encouraging as the prospect may sound, making commercial supersonic flight a reality, faces many challenges. Getting an aircraft to above Mach speeds requires seven to nine times the amount of fuel needed for "normal" subsonic flight, increasing fuel costs by 25 times compared to aircraft using regular fuel [3]. Sustainable aviation fuel comes with limited supply and high costs, and scientists predict zero profit for companies using it under most conditions [3].

Therefore, even if a supersonic jetliner was introduced to the public, it would be for the elite few. To accomplish Overture's goal of being net-zero, its ticket prices have to be sky-high (no pun intended) and if it should prioritise wide-spreading, it will have to compromise on being environmentally friendly by using kerosene and other regular fossil-based fuels.

Sound waves of an aircraft
Image credits: @nasaaero on Instagram

References

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Gut-Feelings

Many call it our second **brain**, or our **little** brain, and just like our primary brain, of which the **complexity** is seen in the **non-linearity** of its neural connections, our enteric system is not of easier understanding. And if this might already seem of **challenging** research, its relation and impact on the **central nervous system** is also difficult to depict.

Our **enteric** nervous system is located in our gut and arose in **evolution** through the symbiotic relation between bacteria, which now constitute our **microbiome**, and our **ancestors** who would benefit from the substances secreted by these bacteria and the **signalling molecules** they produce. In fact, all animals today have a microbiome. These bacteria are essential for **digestion** and for bottom-up signals from the gut to our brain, mainly through the **vagus nerve**. In the same way, a 'bad' or imbalanced microbiome composition has detrimental effects on our **digestive system**, as well as on our central nervous system, to an extent which is not yet fully understood by science.

BUT WHAT HAPPENS WHEN THERE ARE IMPAIRMENTS ALONG THE GUT-BRAIN AXIS?

The **communications** between the gut and the brain are predominantly regulated by bidirectional **neuroendocrine** pathways. An example is **glucagon-like-peptide-1** (GLP-1), a key regulator for gastric emptying and motility, of which the secretion seems to be reduced after **gut-brain-axis** impairment, i.e. after traumatic brain injury. This results in a reduced sensation of fullness after eating. We can therefore **hypothesise** that disturbances of the gut-brain axis lead to unreliable internal regulatory cues, through an **imbalance** of the sensations of fullness or hunger. In addition, gastric dysmotility leads to general **discomfort**, which often culminates in a **distorted perception** of our bodies. The difficult challenge is therefore that of discerning between the **physiological** effects on the central nervous system of the diseases, and the psychological variables deriving from the gut-brain axis impairment.

Recent studies and evidence from the **patient** population have shown that diseases and **disorders** arising from the impairment of the gut-brain axis, affecting both the enteric nervous system and the central nervous system, are rising in patient numbers. One of these diseases, which seems to have a strong interlink with psychological variables, is **irritable-bowel-syndrome** (IBS). At least 12% of the UK population is affected by IBS, but the percentage might be higher if we consider its **poor clinical coding** and assessment. It has become a common **public health issue** among university students, impacting their physical and mental health. It is a functional digestive disorder, like functional **dyspepsia**, of chronic and relapsing nature. It is linked with **chronic pain**, and the painful gut sensation arises by electrical signal transmission from the **enterochromaffin** cells along the gut lumen to the central nervous system. Studies show its link with lower concentration of **protein-YY**, a key regulator of gastric motility through its action on **serotonin**, in certain parts of the intestinal tract. The lower serotonin production leads to gastric dysmotility. This, and perhaps other variables, lead to a general **inflammatory** state and an immune system weakening, with a progressive loss of T-cells, which are central elements in broader **immune** responses.

The disorder is difficult to treat with **conventional** medicine, due to it mostly failing to intervene in diseases that arise from multiple **dysfunctions**. In addition, **pain** is one of the most difficult symptoms to treat, as it is uniquely felt by the patients, and psychological variables have a great impact, even if pathologies linked with the gut-brain axis are not considered. In general, chronic pain is of **difficult treatment** and has been in the spotlight for controversies. For example, opioids have been used to treat chronic pain, although it is now thought that pain is

increased as a **side-effect** after prolonged opioid use. In fact, opioid-deriving drugs are beneficial for acute pain treatment, but are not indicated for chronic pain, besides being infamous for their **addictive** properties, as seen in the opioid crisis in the US in the '90s. The future of chronic pain treatment could either derive from the development of different target pain **receptor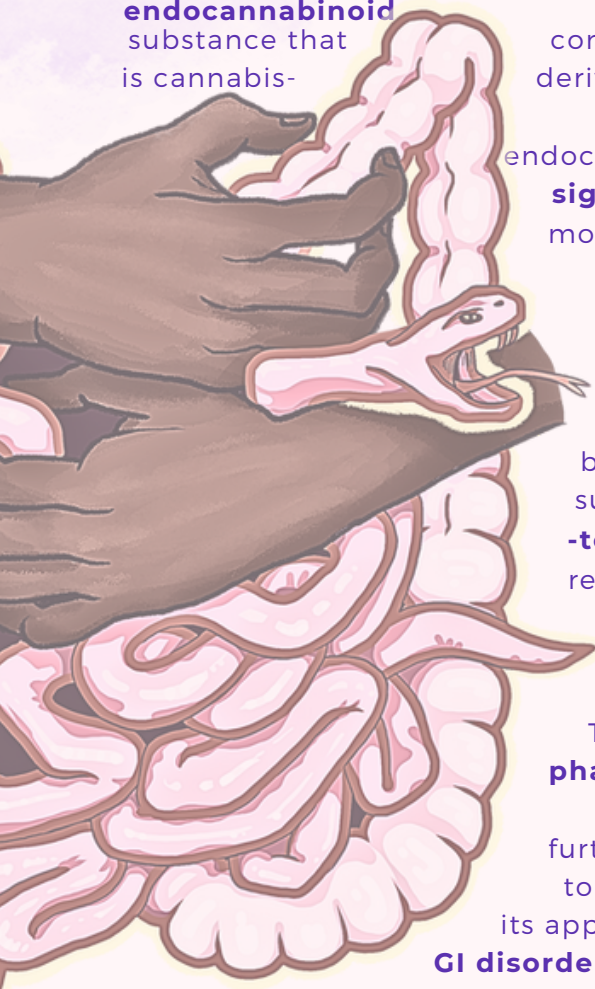-modulating** drugs, or from alternative **therapies**, such as deep-brain stimulation (DBS), in which brain areas linked to pain are targeted to modify pain perception. This **technique** is of promising application for patients in which **pharmacological** treatment does not seem effective, although DBS opens **ethical** concerns regarding its effects on cognition, especially cognitive enhancement. Furthermore, it cannot be forgotten that some of its early advances in the last century stem from a **history of abuse**. DBS development is however encouraged by trial grants, especially in the field of neuropathic pain. Although these **alternative** techniques seem promising, it is still important to also keep encouraging the exploitation of our **natural** pain blockers, our opioid receptors, to eradicate chronic pain.

Our bodies, in fact, possess an internal pain-modulating system, the **endocannabinoid system** (ECS), which is naturally a binding site for endogenous molecules like **enkephalins** and **endorphins**, involved in pain transmission to the central nervous system for perception and modulation. Existing
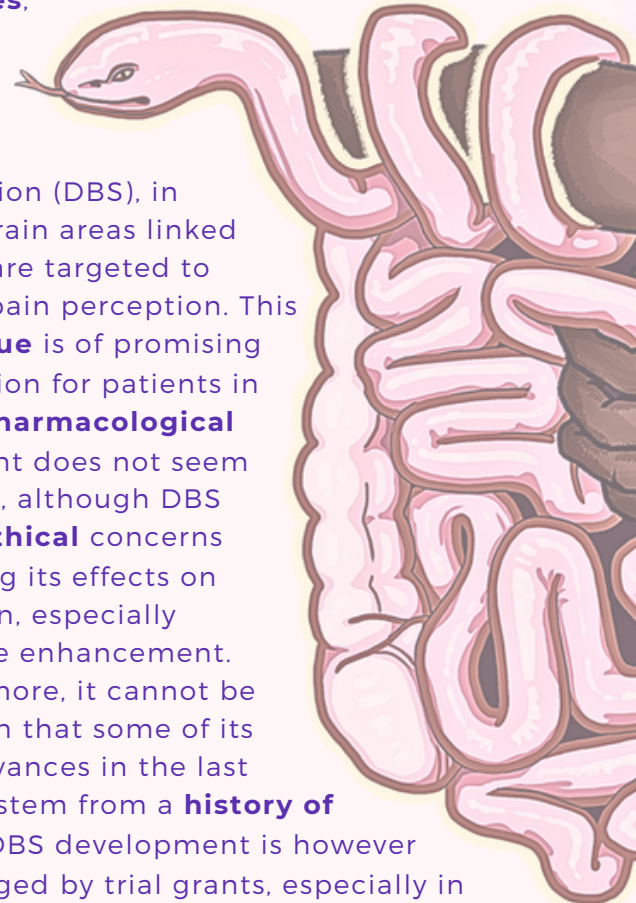
phase II trial drug Olorinab acts directly on the ECS receptor CB2 and is showing promising effects on visceral analgesia, which could be exploited for IBS visceral hypersensitivity. Although for now, it seems more effective than placebo in IBS, the measurements are not to the desired threshold. Talking about the endocannabinoid system, a substance that comes to mind is cannabis-derived CBD, as this inhibits endocannabinoid signalling: the molecule does not bind to endocanna--binoid receptors directly, but to others such as sero--tonin, opioid receptors and G-protein coupled receptors. Therefore its pharmacology needs to be further defined to understand its applications on GI disorder treatment. Larger trials are needed to understand the efficacy of exploiting the EC pain circuit, although there needs to be some caution taken when considering this system, as some single gene polymorphism in the ECS seem to be linked with higher psychiatric susceptibility. On the other hand, ECS-activating drugs seem, on animal models, also acting on the immune cells of the gut mucosa, therefore exhibiting immuno-protective functions on the GI tract. Exploiting this neuromodulatory pathway could lead to exceptional treatments, but more research needs to be carried out to fully evaluate the benefits and possible risks of the ECS.

Other than pain, one of the most common complications associated with gastrointestinal disorders is inflammation. This can particularly be seen in leaky gut syndrome: the name derives from the fact that the internal mucosal cavity of the intestinal tract is in an inflammatory state which causes it to 'leak' molecules into the abdominal cavity. The epithelial permeability is increased as a result of increased paracellular transport mechanisms, transcellular permeability and cell lining apoptosis. The disease is a result of microbiotic impairment and its effects are not only linked to the gut, as the whole immune system is in a 'stressed state' due to the weakened compartmentalisation of molecules. Importantly, there is evidence that the disease is linked with Parkinson's disease onset: the disease is in fact characterised by intraneuronal accumulations of alpha-synuclein protein, and evidence has shown that this protein production could start from the gut and then travel to dopaminergic neurons in the central nervous system through the gut-brain axis, leading to Parkinson's onset.

Nowadays, our understanding of the connection between the central and enteric nervous system leads us also to hypothesise that functional gastrointestinal impairments impact our mood, stress and mental health and vice versa. There are therefore bottom-up and top-down aspects of the disorders which need greater investigation. In fact, although many studies claim that poor digestive health leads to mental health issues, such as anxiety and depression, most studies have been done on animal models, in which mood disorder results are arguably of broad interpretation. Undeniably, however, the disorder's symptoms are related to the ones seen in anxiety and depression in humans.

There are other **points** to have in mind when considering the correlation between **mental** health and **gastrointestinal** disorders. First of all, gastrointestinal **disorders** are generally underdiagnosed, and usually, **patients** who will talk to a GP are only the ones who show the greatest **distress** towards the symptoms and have more complications. In addition, it is difficult to evaluate the **causal link** between a **pathology** of which we do not know the origin and other diseases. In fact, the **credibility** of the correlation is undermined by the initial lack of **understanding** of the factors that cause visceral hypersensitivities, chronic pain and immune system **inflammations** in gastrointestinal disorders in the first place. This said, although there is difficulty in **establishing** a clear link between gastrointestinal disorders and mood disorders, their **impact** on one another is undeniable. For example, IBS reportedly impacts patients' **life quality** in all aspects, such as eating, sleeping, cognitive focus, time management, sex, and physical appearance. When described, it is both cited as an **insecurity** and as a stress-causing disorder.

When considering the **consequences** of distress, it is not only our **mood** that is affected, but also our insight of the **surrounding**, which shapes our **perspective** on the particular **circumstances** we live in. In our everyday life we sometimes experience instances of **'deeper knowing'** in which we make decisions without **reasoning**: these moments of intuition are said to be linked with quick and effective **recalling** of past **events** and sensations, which can be registered in our **gut** through the distress or other **emotion** an event arose in us. Although there is no scientific evidence for the so-called **'gut-feelings'**, we can hypothesise that an impaired gut-brain axis leads to **excessive distress** and discomfort spread across our memories and to some sort of **disconnection**.

Disconnection from the centre of our body, from our core, from our instincts and feelings, and disconnection from others as a result of **chronic pain**. When someone experiences constant dull pain, our body and mind have one **priority**: to fight back the feeling. This leads to a deep **focus** on our pain, as it is the body's primary **interest** to reverse the situation. Consequently, our engagement and **carefree** relation with the external events are **diminished**. In addition, it is even more difficult to engage with the **surrounding** people, as it is often difficult to express the pain felt, as we can't **articulate** it, or see it, as neurobiologist **Allan Basbaum**, from the University of California stated: that's perhaps why often pain is better illustrated through **art**, and fields like **neuroaesthetics** are trying to understand pain **sensations** better through these alternative artistic illustrations.

Evidence suggests that **disconnection** consequent to pain can be reduced through **movement**. Or **stillness**. As opposite as these two concepts could seem, from Oriental practices we can see

that it is their balance that can root us back to our bodies, by both **contrasting** ourselves with the outside, as well as **connecting** ourselves with the surroundings. In the instance of **IBS**, which we have seen is linked to stress and **anxiety** feelings, whether or not they are a cause or consequence of the disorder, it is clear that our **thoughts** are part and impact factor of the disorder's pain. As UCLA Professor Dr. Emeran Mayer, a distinguished researcher in the mind-gut **connection**, stated, "we have the power to engineer our internal **ecosystem**, and our bodies and minds. Obviously, it is not an easy process, considering the **everyday** life constraints we face, but it is undeniable that our thoughts are a powerful tool that can overwrite the **distressing** unconscious sensations: probably not enough to reverse chronic pain, but probably enough to sometimes feel **harmony** between our minds and bodies.

References